

**20-1025 (Lead); 20-1138 (Consolidated)**

---

**UNITED STATES COURT OF APPEALS  
FOR THE DISTRICT OF COLUMBIA CIRCUIT**

---

ENVIRONMENTAL HEALTH TRUST; CONSUMERS FOR SAFE CELL  
PHONES; ELIZABETH BARRIS; THEODORA SCARATO

CHILDREN’S HEALTH DEFENSE; MICHELE HERTZ; PETRA BROKKEN;  
DR. DAVID O. CARPENTER; DR. PAUL DART; DR. TORIL H. JELTER; DR.  
ANN LEE; VIRGINIA FARVER, JENNIFER BARAN; PAUL STANLEY, M.Ed.  
*Petitioners*

v.

FEDERAL COMMUNICATIONS COMMISSION;  
UNITED STATES OF AMERICA  
*Respondents*

---

Petition for Review of Order Issued by the  
Federal Communications Commission

---

**DEFERRED JOINT APPENDIX**

**VOLUME 14**

Edward B. Myers  
Law Office of Edward B. Myers  
14613 Dehaven Court  
North Potomac, MD 20878  
Phone: 717-752-2032  
[edwardbmyers@yahoo.com](mailto:edwardbmyers@yahoo.com)

*Counsel for Petitioners 20-1025*

Robert F. Kennedy, Jr.  
Children’s Health Defense  
1227 North Peachtree Pkwy #202  
Peachtree City, GA 30269  
Phone: 845-377-0211  
[rfk.fcc@childrenshealthdefense.org](mailto:rfk.fcc@childrenshealthdefense.org)

W. Scott McCollough  
McCollough Law Firm, P.C.  
2290 Gatlin Creek Rd.  
Dripping Springs, TX 78620  
Phone: 512-888-1112  
[wsmc@dotlaw.biz](mailto:wsmc@dotlaw.biz)

*Counsel for Petitioners 20-1138*

## INDEX TO DEFERRED APPENDIX

Tab No.	JA Page Nos.	Date	Filer/Author	Filing/Attachment Description
<b>VOLUME 1 – Tabs 1-2</b>				
<b>COMMISSION ORDER AND NOTICE OF INQUIRY</b>				
1	1-160	Dec. 4, 2019	FCC	<i>Resolution of Notice of Inquiry Order</i>
2	161-363	Mar. 29, 2013	FCC	<i>Notice of Inquiry</i>
<b>VOLUME 2 – Tabs 3 – 7 Part 1</b>				
<b>COMMENTS AND OTHER FILINGS</b>				
3	364-428	Sep. 3, 2013	CTIA-The Wireless Association	FCC; Comments of the CTIA - The Wireless Association, ET Docket No. 13-84
4	429-467	Nov 18, 2013	CTIA-The Wireless Association	FCC; Reply Comments of the CTIA - The Wireless Association, ET Docket No. 13-84
5	468-572	Sep. 3, 2013	Mobile Manufacturers Forum	FCC; Mobile Manufacturers Forum Comments, ET Docket No. 13-84
6	573-588	Nov. 18, 2013	Mobile Manufacturers Forum	FCC; Mobile Manufacturers Forum Reply Comments, ET Docket No. 13-84

## INDEX TO DEFERRED APPENDIX

<b>Tab No.</b>	<b>JA Page Nos.</b>	<b>Date</b>	<b>Filer/Author</b>	<b>Filing/Attachment Description</b>
7 Part 1	589-764	Sep. 16, 2019	Joel M. Moskowitz PhD	Research Compilation; Abstracts of over 2,100 studies published between 1990 - 2017; Prof. Henry Lai. (Tab 7 Part 1)
<b>VOLUME 3 – Tab 7 Part 2</b>				
7 Part 2	765-1164	Sep. 16, 2019	Joel M. Moskowitz PhD	Research Compilation; Abstracts of over 2,100 studies published between 1990 - 2017; Prof. Henry Lai.(Tab 7 Part 2)
<b>VOLUME 4 – Tab 7 Part 3</b>				
7 Part 3	1165-1564	Sep. 16, 2019	Joel M. Moskowitz PhD	Research Compilation; Abstracts of over 2,100 studies published between 1990 - 2017; Prof. Henry Lai.(Tab 7 Part 3)
<b>VOLUME 5 – Tabs 7 Part 4 – 8 Part 1</b>				
7 Part 4	1565-1602	Sep. 16, 2019	Joel M. Moskowitz PhD	Research Compilation; Abstracts of over 2,100 studies published between 1990 - 2017; Prof. Henry Lai.(Tab 7 Part 4)
8 Part 1	1603-1964	Sep. 13, 2019	Joel M. Moskowitz PhD	Research Compilation; Abstracts of Over 600 Studies Published Between August 2016- August 2019, Dr. Joel Moskowitz; 2019 (Tab 8 Part 1)

## INDEX TO DEFERRED APPENDIX

<b>VOLUME 6 – Tabs 8 Part 2 - 10</b>				
8 Part 2	1965-2130	Sep. 13, 2019	Joel M. Moskowitz PhD	Research Compilation; Abstracts of Over 600 Studies Published Between August 2016- August 2019, Dr. Joel Moskowitz; 2019 (Tab 8 Part 2)
9	2131-2142	Sep. 28, 2016	Gary C. Vesperman	Research Compilation; Abstracts of 15 New Studies, Dr. Joel Moskowitz PhD, 2016
10	2143-2378	Jul. 7, 2016	Environmental Health Trust	Research Compilation; Studies and Documents; City of Pinole, CA
<b>VOLUME 7 – Tabs 11 – 13 Part 1</b>				
11	2379-2389	Jul. 7, 2016	Environmental Health Trust	US Exposures Limits - A History of Their Creation, Comments and Explanations; Eng. Lloyd Morgan
12	2390-2439	Aug. 26, 2016	Heidi M. Lumpkin	Biosystem & Ecosystem; Birds, Bees and Mankind: Destroying Nature by ‘Electrosmog’: Effects of Mobile Radio and Wireless Communication. Dr. Ulrich Warnke, Ph.D., 2007
13 Part 1	2440-2778	Jul. 13, 2016	Parents for Safe Technology	Cancer; IARC Monograph: Non-Ionizing Radiation Part 2: RF EMFs, 2013 (Tab 13 Part 1)
<b>VOLUME 8 – Tabs 13 Part 2 - 23</b>				
13 Part 2	2779-2920	Jul. 13, 2016	Parents for Safe Technology	Cancer; IARC Monograph: Non-Ionizing Radiation Part 2: RF EMFs, 2013 (Tab 13 Part 2)



## INDEX TO DEFERRED APPENDIX

14	2921-2927	Nov. 18, 2013	Kevin Mottus	Cancer; IARC Press Release: IARC Classifies RF EMFs As Possibly Carcinogenic to Humans, 2011
15	2928-3002	Jul. 11, 2016	Environmental Health Trust	NTP; Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposures); Draft 5-19-2016
16	3003-3009	Oct. 1, 2018	Environmental Health Trust	NTP; Commentary on the utility of the National Toxicology Program study on cell phone radiofrequency radiation data for assessing human health risks despite unfounded criticisms aimed at minimizing the findings of adverse health effects. Environmental Research. Dr. Ron Melnick; 2019
17	3010-3036	Apr. 16, 2018	Theodora Scarato	NTP; Dr. Hardell and Dr. Carlsberg letter to the NTP, NIH, DHHS, NTP Technical Report On The Toxicology And Carcinogenesis Studies; Mar. 12, 2018
18	3037-3048	Oct. 1, 2018	Environmental Health Trust	Cancer-NTP; Cancer epidemiology update, following the 2011 IARC evaluation of radiofrequency electromagnetic fields; (Miller et al); 2018
19	3049-3055	Oct. 18, 2018	Joel M. Moskowitz, Ph.D.	Cancer-NTP; The Significance of Primary Tumors in the NTP Study of Chronic Rat Exposure to Cell Phone Radiation. IEEE Microwave Magazine. Prof. James C. Lin; 2019

## INDEX TO DEFERRED APPENDIX

20	3056-3065	Aug. 27, 2013	Cindy Sage and David O. Carpenter	BioInitiative Comments
21	3066-3080	Nov. 18, 2013	Kevin Mottus	BioInitiative; 2012 Conclusions
22	3081-3126	Nov. 18, 2013	Kevin Mottus	BioInitiative; Section 24: Key Scientific Evidence and Public Health Policy Recommendations; 2012
23	3127-3146	Jul. 11, 2016	Cecelia Doucette	BioInitiative; Section 1: Summary for the Public (2014 Supplement)
<b>VOLUME 9 – Tabs 24-27</b>				
24	3147-3218	Sep. 30, 2016	Catherine Kleiber	BioInitiative-Modulation; Section 15: Evidence for Disruption by Modulation Role of Physical and Biological Variables in Bioeffects of Non-Thermal Microwaves for Reproducibility, Cancer Risk and Safety Standards, (2012 Supplement)
25	3219-3319	Sep. 3, 2013	Kevin Mottus	BioInitiative; Section 20, Findings in Autism, Consistent with Electromagnetic Fields (EMF) and Radiofrequency Radiation (RFR); 2012
26	3320-3321	Sep. 16, 2019	Joel Moskowitz PhD.	BioInitiative-Neurological; Percent Comparison, Effect vs No Effect in Neurological Effect Studies; 2019
27	3322-3559	Sep. 16, 2019	Joel Moskowitz PhD.	BioInitiative-Neurological; Research Summaries, RFR Neurological Effects (Section 8), 2007-2017; 2017

## INDEX TO DEFERRED APPENDIX

<b>VOLUME 10 – Tabs 28-41</b>				
28	3560-3561	Sep. 16, 2019	Joel M. Moskowitz PhD.	BioInitiative-Mechanisms of Harm; Percent Comparison Showing Effect vs No Effect, DNA (Comet Assay), 2017 and Free Radical (Oxidative Stress), 2019
29	3562-3602	Sep. 16, 2019	Joel M. Moskowitz PhD.	BioInitiative-Mechanisms of Harm; Research Summaries, DNA (Comet Assay) Studies; 76 Studies, 2017
30	3603-3721	Sep. 16, 2019	Joel M. Moskowitz PhD.	BioInitiative-Mechanisms of Harm; Research Summaries, Free Radicals (Oxidative Stress Effects), 225 studies, 2019
31	3722-3749	Apr. 11, 2014	Cindy Sage, MA	BioInitiative Working Group; Preliminary Opinion on Potential Health Effects of Exposure to Electromagnetic Fields (EMF); 2014
32	3750-3755	Sep. 16, 2019	Bioinitiative Working Group	BioInitiative Working Group; Consistent Failure to Identify the Potential for Health Effects (Exhibit A); 2014
33	3756-3766	Sep. 14, 2019	Bioinitiative Working Group	BioInitiative Working Group; Reference List for Important Fertility and Reproduction Papers (Exhibit C); 2014
34	3767-3771	Apr. 14, 2019	Cindy Sage	BioInitiative Working Group; Mitochondrial Dysfunction and Disruption of Electrophysiology (Exhibit G); 2014

## INDEX TO DEFERRED APPENDIX

35	3772-3779	Apr. 14, 2019	Cindy Sage, MA	BioInitiative Working Group; Epidemiological Studies, RF fields epidemiology, Comments by Drs. Lennart Hardell, Fredrik Soderqvist PhD. and Michael Carlberg, MSc. Section 3.5.1.1 Epidemiological Studies (Exhibit B); 2014
36	3780-3874	Apr 11, 2014	Cindy Sage, MA	BioInitiative Working Group; An Update on the Genetic Effects of Nonionizing Electromagnetic Fields by Prof. Henry Lai PhD; (Exhibit E); 2014
37	3875-3896	Apr. 11, 2014	Cindy Sage, MA	BioInitiative Working Group; An Update on Physical and Biological Variables, Cancer and Safety Standards by Prof. Igor Belyaev Dr. Sc., (Exhibit F); 2014
38	3897-3904	Sep. 30, 2016	Maria Powell	BioInitiative Co-Editor; Human Health Effects of EMFs: The Cost of Doing Nothing. IOPScience. (Prof. David Carpenter MD.); 2010
39	3905-3919	Sep. 28, 2016	Kevin Mottus	BioInitiative Author; Statement of Prof. Martin Blank PhD., PhD.; 2016
40	3920-3945	Aug 27, 2013	Sage Hardell Herbert	BioInitiative Authors; Prof. Lennart Hardell MD. PhD., Prof. Martha Herbert MD. PhD. and Cindy Sage Comments
41	3946-3984	Aug. 26, 2013	B. Blake Levitt & Henry Lai	BioInitiative Author; Prof. Henry Lai PhD, and Blake Levitt Comments

## INDEX TO DEFERRED APPENDIX

<b>VOLUME 11 – Tabs 42-59</b>				
42	3985-4072	Sep. 3, 2013	Paul Dart MD	Dr. Paul Dart MD. (Petitioner) Comments
43	4073-4102	Feb. 4, 2013	Dr. Andrew Goldsworthy	The Biological Effects of Weak Electromagnetic Fields, Problems and Solutions, Prof. Andrew Goldsworthy; 2012
44	4103-4106	Sep. 4, 2013	Richard Meltzer	Dr. Richard Meltzer Comments, Radio Frequency (RF) Exposure: A Cautionary Tale
45	4107-4112	Feb. 6, 2013	Donald R. Maisch	Dr. Donald R. Maisch PhD. Comments
46	4113-4129	Nov. 18, 2013	Catherine Kleiber	Biological Effects from RF Radiation at Low-Intensity Exposure, based on the BioInitiative 2012 Report, and the Implications for Smart Meters and Smart Appliances; Dr. Ron M. Powell, PhD.; 2013
47	4130-4137	Aug. 20, 2013	Lawrence James Gust	Eng. Lawrence James Gust Comments
48	4138-4146	Feb. 25, 2013	Michael Schwaebe	Eng. Michael Schwaebe Comments
49	4147-4178	Mar. 18, 2015	Environmental Working Group	Organizations; Environmental Working Group Reply Comments
50	4179-4195	Nov. 18, 2013	Nina Beety	Nina Beety Comments

## INDEX TO DEFERRED APPENDIX

51	4196-4206	Sep. 16, 2019	Joel Moskowitz PhD.	Organizations; EMF Scientist Appeal, International Scientists' Appeal to the United Nations; 2015
52	4207-4217	Apr. 5, 2018	NancyD	Organizations; 5G Appeal, Scientist Appeal to the EU, Scientists Warn of Potential Serious Health Effects of 5G; 2017
53	4218-4240	Jun. 7, 2017	Environmental Health Trust	Organizations; Medical Doctors and Public Health Organizations: Consensus Statements and Doctors' Recommendations on Cell Phones/Wireless; 2017
54	4241-4244	Sep. 27, 2016	Kevin Mottus	Organizations; Council of Europe, Résolution 1815, The Potential Dangers of Electromagnetic Fields and Their Effect on the Environment; 2011
55	4245-4257	Feb. 5, 2013	Gilda Oman	Organizations; Council of Europe, Parliamentary Assembly Report: The potential dangers of electromagnetic fields and their effect on the environment; 2011
56	4258-4293	Jul. 11, 2016	Environmental Health Trust	Organizations - Radiation Sickness; European Academy for Environmental Medicine, EUROPAEM EMF Guideline 2015 for the prevention, diagnosis and treatment of EMF-related health problems and illnesses; 2015

## INDEX TO DEFERRED APPENDIX

57	4294-4305	Feb. 5, 2013	David Mark Morrison	Organizations; Scientific Panel on Electromagnetic Field Health Risks: Consensus Points, Recommendations, and Rationales, Scientific Meeting: Seletun, Norway. Reviews on Environmental Health; (Fragopoulou, Grigoriev et al); 2010
58	4306-4361	Aug. 30, 2013	EMF Safety Network	Organizations; EMF Safety Network Comments
59	4362-4374	Jul 7, 2016	Environmental Health Trust	Organizations - Russian Government; Electromagnetic Fields From Mobile Phones: Health Effect On Children And Teenagers   Resolution Of Russian National Committee On Nonionizing Radiation Protection   April 2011, Moscow
<b>VOLUME 12 – Tabs 60 – 68 Part 1</b>				
60	4375-4482	Jul 7, 2016	Environmental Health Trust	Organizations - Cyprus Government; Neurological and behavior effects of Non-Ionizing Radiation emitted from mobile devices on children: Steps to be taken ASAP for the protection of children and future generations. Presentation Slides; 2016
61	4483-4531	Nov. 18, 2013	Kevin Mottus	Organizations; Austrian Medical Association, Environmental Medicine Evaluation of Electromagnetic Fields; Dr. Jerd Oberfeld MD.; 2007
62	4532-4534	Jul. 11, 2016	Environmental Health Trust	Organizations; The American Academy of Pediatrics, Letter to the FCC; 2013

## INDEX TO DEFERRED APPENDIX

63	4535-4540	Sep. 29, 2016	Kevin Mottus	Organizations; California Medical Association, House of Delegates Resolution Wireless Standards (Resolution 107 - 14); 2014
64	4541-4543	Sep. 3, 2013	Grassroots Environmental Education, Inc. o/b/o American Academy of Environmental	Organizations; American Academy of Environmental Medicine, Letter to the Federal Communications Commission; 2013
65	4544-4561	Sep. 29, 2016	Kevin Mottus	Organizations - Radiation Sickness; Austrian Medical Association, Guidelines for the Diagnosis and Treatment of EMF Related Health Problems and Illnesses (EMF Syndrome); 2011
66	4562-4590	Sep. 28, 2016	Kevin Mottus	Organizations; International Association of Fire Fighters, Position on the Health Effects from Radio Frequency/Microwave Radiation in Fire Department Facilities from Base Stations for Antennas and Towers; 2004
67	4591-4599	Sep. 28, 2016	Kevin Mottus	Organizations; Cities of Boston and Philadelphia Reply Comments
68 Part 1	4600-4800	Sep. 3, 2013	Environmental Working Group	Organizations; Appeal to the FCC Signed by 26,000 People and Organized by the Environmental Working Group, 2013 (Tab 68 Part 1)



## INDEX TO DEFERRED APPENDIX

<b>VOLUME 13 – Tabs 68 Part 2 - 76</b>				
68 Part 2	4801- 5171	Sep. 3, 2013	Environmental Working Group	Organizations; Appeal to the FCC Signed by 26,000 People and Organized by the Environmental Working Group, 2013 (Tab 68 Part 2)
69	5172- 5186	Aug. 25, 2016	Kevin Mottus	Organizations; Freiburger Appeal - Doctors Appeal; 2002
70	5187- 5191	Sep. 3, 2013	Grassroots Environmental Education, Inc.	Organizations; Benevento Resolution, The International Commission for Electromagnetic Safety (ICEMS), 2006
71	5192- 5197	Jul. 18, 2016	Environmental Health Trust	Organizations; The Porto Alegre Resolution; 2009
72	5198- 5204	Feb. 6, 2013	Kevin Mottus	Organizations; Kaiser Permanente, Letter from Dr. De-Kun Li, Division of Research
73	5205- 5210	Sep. 3, 2013	American Association For Justice	Organizations; American Association for Justice, Comments
74	5211- 5219	Feb. 6, 2013	Jonathan Libber	Organizations; Maryland Smart Meter Awareness, Comments (filed by Jonathan Libber)
75	5220- 5228	Feb. 6, 2013	Electromagnetic Safety Alliance	Organizations; Electromagnetic Safety Alliance, Comments

## INDEX TO DEFERRED APPENDIX

76	5229-5241	Sep. 29, 2016	Ed Friedman	Organizations; Wildlife and Habitat Conservation Solutions; What We Know, Can Infer, and Don't Yet Know about Impacts from Thermal and Non-thermal Non-ionizing Radiation to Birds and Other Wildlife. Dr. Albert M. Manville, PhD.; 2016
<b>VOLUME 14 – Tabs 77-96</b>				
77	5242-5258	Sep. 30, 2016	Catherine Kleiber	Mechanisms of Harm; Meta-Analysis, Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn Biol Med (Yakymenko et al); 2016
78	5259-5269	Sep 3, 2013	Monnie Ramsell	Mechanisms of Harm; Blood Brain Barrier; Increased Blood–Brain Barrier Permeability in Mammalian Brain 7 Days after Exposure to the Radiation from a GSM-900 Mobile Phone. Pathophysiology (Nittby, Salford et al); 2009
79	5270-5286	Sep. 3, 2013	Paul Dart MD.	Mechanisms of Harm; DNA Damage; Microwave RF Interacts with Molecular Structures; Dr. Paul Dart MD.; 2013
80	5287-5303	Sep. 3, 2013	The EMR Policy Institute	Medical Treatments & Modulation; Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. British Journal of Cancer. (Costa et al); 2011

## INDEX TO DEFERRED APPENDIX

81	5304-5306	Sep. 3, 2013	The EMR Policy Institute	Medical Treatments & Modulation; Treating cancer with amplitude-modulated electromagnetic fields: a potential paradigm shift, again? British Journal of Cancer. (Dr. Carl Blackman); 2012
82	5307-5309	Feb. 8, 2013	Alan Frey	Modulation; Dr. Alan Frey PhD., Comments, Feb. 7, 2013
83	5310-5319	Jul. 11, 2016	Environmental Health Trust	Modulation; Real Versus Simulated Mobile Phone Exposures in Experimental Studies. Biomed Res Int. (Prof. Panagopoulos et al); 2015
84	5320-5368	Sep. 16, 2019	Joel M. Moskowitz, PhD	Neurological; Book Chapter, A Summary of Recent Literature (2007-2017) on Neurological Effects of Radiofrequency Radiation, Prof. Lai; 2018 Referenced 122 Studies.
85	5369-5412	Sep. 28, 2016	Kevin Mottus	Neurological - Report; Evidence of Neurological effects of Electromagnetic Radiation: Implications for degenerative disease and brain tumour from residential, occupational, cell site and cell phone exposures. Prof. Neil Cherry; 225 scientific references. 2002
86	5413-5415	Sep 3, 2013	Kevin Mottus	Neurological; The effects of mobile-phone electromagnetic fields on brain electrical activity: a critical analysis of the literature. Electromagn Biol Med. (Marino et al) (Abstract); 2009

## INDEX TO DEFERRED APPENDIX

87	5416-5435	Nov. 18, 2013	Kevin Mottus	Autism and EMF? Plausibility of a pathophysiological link. Pathophysiology, Part I. (Herbert et al); 2013
88	5436-5460	Nov. 18, 2013	Kevin Mottus	Autism and EMF? Plausibility of a pathophysiological link. Pathophysiology, Part II. (Herbert et al); 2013
89	5461-5486	Sep. 3, 2013	Kevin Mottus	Fertility; Research Abstracts, List of References Reporting Fertility and/or Reproduction Effects from Electromagnetic Fields and/or Radiofrequency Radiation (66 references)
90	5487-5499	Sep. 3, 2013	Paul Dart MD	Fertility; Effects of Microwave RF Exposure on Fertility, Dr. Paul Dart MD. (Petitioner); 2013
91	5500-5506	Sep. 3, 2013	Paul Dart MD	Hormonal; RF and Hormones, Alterations in Hormone Physiology; Dr. Paul Dart MD. (Petitioner); 2013
92	5507-5514	Feb. 7, 2013	Toni Stein	Prenatal & Children; Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice. Scientific Reports. (Aldad, Taylor et al); 2012
93	5515-5518	Jul. 7, 2016	Environmental Health Trust	Prenatal & Children; Fetal Exposures and Cell Phones. Studies List. Prof. Hugh Taylor MD.; 2015

## INDEX TO DEFERRED APPENDIX

94	5519-5553	Jul. 13, 2016	Parents for Safe Technology	Prenatal and Children; Fetal Cell Phone Exposure: How Experimental Studies Guide Clinical Practice, Hugh S. Taylor MD. PhD., Chair of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine
95	5554-5559	Sep. 3, 2013	Dr. Suleyman Kaplan	Prenatal & Children; Dr. Suleyman Kaplan Comments
96	5560-5614	Nov. 18, 2013	Kevin Mottus	Prenatal & Children; Amended Declaration of Dr. David O. Carpenter MD. (Dec. 20, 2011); <i>Morrison et al v. Portland Schools</i> , No. 3:11-cv-00739-MO (U.S.D.C. Oregon, Portland Div.)
<b>VOLUME 15 – Tabs 97-101</b>				
97	5615-5712	Sep. 28, 2016	Kevin Mottus	Prenatal & Children; Doctors and Scientists Letters on Wi-Fi in Schools
98	5713-5895	Jul. 11, 2017	Environmental Health Trust	Dr. Devra Davis PhD., President of Environmental Health Trust (Petitioner) Comments
99	5896-5993	Jun. 7, 2017	Environmental Health Trust	Children; Letter to Montgomery County Schools, Prof. Martha Herbert MD., PhD.; 2015
100	5994-6007	Apr. 29, 2019	Environmental Health Trust	Neurological - Children; A Prospective Cohort Study of Adolescents' Memory Performance and Individual Brain Dose of Microwave Radiation from Wireless Communication. Environ Health Perspect. (Foerster et al); 2018

## INDEX TO DEFERRED APPENDIX

101	6008-6014	Sep. 28, 2016	Kevin Mottus	Prenatal & Children; Cell phone use and behavioral problems in young children. J Epidemiol Community Health. (Divan et al); 2012
<b>VOLUME 16 - Tabs 102-126</b>				
102	6015-6026	Jul. 7, 2016	Environmental Health Trust	Prenatal & Children; “Cell Phones & WiFi – Are Children, Fetuses and Fertility at Risk?”; 2013
103	6027-6060	Jul. 7, 2016	Environmental Health Trust	Prenatal & Children; Safe Schools 2012, Medical and Scientific Experts Call for Safe Technologies in Schools
104	6061-6067	Sep. 3, 2013	Kevin Mottus	Prenatal & Children - Stem Cells; Microwaves from Mobile Phones Inhibit 53BP1 Focus Formation in Human Stem Cells More Strongly Than in Differentiated Cells: Possible Mechanistic Link to Cancer Risk. Environmental Health Perspectives (Markova, Belyaev et al); 2010
105	6068-6069	Sep. 26, 2016	Angela Tsaing	Radiation Sickness - Children; Angela Tsiang Comments
106	6070-6071	Mar. 5, 2013	Abigail DeSesa	Radiation Sickness - Children; Abigail DeSesa Comments
107	6072-6111	Sep. 28, 2016	Kevin Mottus	Cell Towers - Research Abstract Compilation; 78 Studies Showing Health Effects from Cell Tower Radio Frequency Radiation; 2016
108	6112-6122	Sep. 3, 2013	Paul Dart MD	Cell Towers; Consequences of Chronic Microwave RF Exposure, Dr. Paul Dart MD. (Petitioner)

## INDEX TO DEFERRED APPENDIX

109	6123-6132	Jul. 11, 2016	Environmental Health Trust	Cell Towers - Cancer; Meta-Analysis, Long-Term Exposure To Microwave Radiation Provokes Cancer Growth: Evidences From Radars And Mobile Communication Systems. (Yakymenko et al); 2011
110	6133-6148	Sep. 3, 2013	Monnie Ramsell	Cell Towers - Neurological; Changes of Clinically Important Neurotransmitters under the Influence of Modulated RF Fields, A Long-term Study under Real-life Conditions; Umwelt-Medizin-Gesellschaft; (Buchner & Eger); 2011
111	6148-6160	Dec. 10, 2018	Environmental Health Trust	Cell Towers - DNA; Impact of radiofrequency radiation on DNA damage and antioxidants in peripheral blood lymphocytes of humans residing in the vicinity of mobile phone base stations. Electromagnetic Biology and Medicine. (Zothansiana et al); 2017
112	6161-6169	Dec. 10, 2018	Environmental Health Trust	Cell Towers - Cancer; Environmental radiofrequency radiation at the Järntorget Square in Stockholm Old Town, Sweden in May, 2018 compared with results on brain and heart tumour risks in rats exposed to 1.8 GHz base station environmental emissions, World Academy of Sciences Journal. (Hardell et al); 2018

## INDEX TO DEFERRED APPENDIX

113	6170-6258	Sep. 30, 2016	Catherine Kleiber	Cell Towers; Indian Government, Ministry of Environment and Forest, Report on Possible Impacts of Communication Towers on Wildlife Including Birds and Bees. 919 studies reviewed; 2011
114	6259-6260	Sep. 3, 2013	Kevin Mottus	Cell Towers; Epidemiological evidence for a health risk from mobile phone base stations, Int J Occup Environ Health. (Hardell et al); 2010
115	6261-6289	Sep. 16, 2019	Joel Moskowitz, PhD	Cell Towers; Biological Effects From Exposure to Electromagnetic Radiation Emitted By Cell Tower Base Stations and Other Antenna Arrays. Environ. Rev. (Lai & Levitt); 2010
116	6290-6301	Jul. 11, 2016	Environmental Health Trust	Cell Towers; Research Summaries of Cell Tower Radiation Studies
117	6302-6311	Sep. 30, 2016	Catherine Kleiber	Cell Towers-Wildlife; Electromagnetic Pollution From Phone Masts. Effects on Wildlife; Pathophysiology. (Dr. Alfonso Balmori); 2009
118	6312-6324	Jul. 18, 2106	Environmental Health Trust	Cell Towers - Wildlife; Testimony of Dr. Albert M. Manville, II, PhD., C.W.B, Before the City of Eugene City Planning Department in Opposition to AT&T/Crossfire's Application for a "Stealth" Cellular Communications Tower; May 6, 2015



## INDEX TO DEFERRED APPENDIX

119	6325-6341	Sep. 30, 2016	Catherine Kleiber	Cell Towers - Plants; Radiofrequency Radiation Injures Trees Around Mobile Phone Base Stations. Science of the Total Environment. (Waldmann-Selsam et al); 2016
120	6342-6349	Apr. 8, 2014	M.K. Hickcox	Biosystem & Ecosystem; The Dangers of Electromagnetic Smog, Prof. Andrew Goldsworthy, PhD.; 2007
121	6350-6366	Sep. 3, 2013	The EMR Policy Institute	Biosystem and Ecosystem; Impacts of radio-frequency electromagnetic field (RF-EMF) from cell phone towers and wireless devices on biosystem and ecosystem – a review. Biology and Medicine (Sivani et al.); 2012
122	6367-6379	Oct. 1, 2018	Environmental Health Trust	5G; 5G wireless telecommunications expansion: Public health and environmental implications, Environmental Research. (Dr. Cindy Russell MD.); 2018
123	6380-6383	Oct. 18, 2019	Joel M. Moskowitz PhD	5G; We Have No Reason to Believe 5G is Safe, Dr. Joel Moskowitz PhD., Scientific American; 2019
124	6384-6392	Jul. 11, 2017	Environmental Health Trust	5G - Millimeter Waves; Nonthermal Effects of Extremely High-Frequency Microwaves on Chromatin Conformation in Cells in vitro—Dependence on Physical, Physiological, and Genetic Factors. IEEEExplore. (Belyaev et al); 2000

## INDEX TO DEFERRED APPENDIX

125	6393-6408	Oct. 1, 2018	Environmental Health Trust	5G; What You Need To Know About 5G Wireless And “Small” Cells Top 20 Facts About 5G; Environmental Health Trust
126	6409-6429	Jan. 13, 2015	NYU Wireless	5G; Millimeter-Wave Cellular Wireless Networks: Potentials and Challenges, IEEE; (2014)
<b>VOLUME 17 – Tabs 127 – 142 Part 1</b>				
127	6430-6436	Jul. 13, 2016	Priscilla King	5G; FCC Chairman Tom Wheeler ‘The Future of Wireless: A Vision for U.S. Leadership in a 5G World’; 2016
128	6437-6447	Jul. 14, 2016	Angela Tsaing	5G; Letter to House Subcommittee on Communications and Technology; Angela Tsiang; 2016
129	6448-6453	Jan. 8, 2019	LeRoy Swicegood	5G; Ask Congress to Vote No, We Are The Evidence Fact Sheet; 2016
130	6454-6510	Jul. 13, 2016	Parents For Safe Technology	5G; 5G Spectrum Frontiers -The Next Great Unknown Experiment On Our Children, Compilation of Letters to Congress; 2016
131	6511-6513	Apr. 16, 2018	Theodora Scarato	5G;What You Need To Know About 5G Wireless and “Small” Cells
132	6514-6587	Sep. 28, 2016	Kevin Mottus	Wi-Fi; 136 Studies Showing Health Effects from Wi-Fi Radio Frequency Radiation

## INDEX TO DEFERRED APPENDIX

133	6588-6603	Jul. 13, 2016	Parents For Safe Technology	Wi-Fi; 2.45-GHz Microwave Irradiation Adversely Affects Reproductive Function in Male Mouse, <i>Mus Musculus</i> by Inducing Oxidative and Nitrosative Stress. Free Radical Research (Shahin et al); 2014
134	6604-6611	Jul. 7, 2016	Environmental Health Trust	Wi-Fi - Fertility; Immunohistopathologic demonstration of deleterious effects on growing rat testes of radiofrequency waves emitted from conventional Wi-Fi devices. Journal of Pediatric Neurology. (Atasoy et al); 2013
135	6612-6620	Apr. 8, 2014	MK Hickox	Smart Meters: Correcting the Gross Misinformation, Letter by 54 Scientists and MDs; 2012
136	6621-6622	Nov. 18, 2013	Catherine Kleiber	Smart Meters - Radiation Sickness; American Academy of Environmental Medicine, Smart Meter Case Series; 2013
137	6623-6692	Sep. 3, 2013	Rachel Cooper	Smart Meters; Assessment of Radiofrequency Microwave Radiation Emissions from Smart Meters; Sage Associates, Environmental Consultants; 2011
138	6693-6699	Jul. 7, 2016	Environmental Health Trust	Smart Meters; FCC Maximum Permissible Exposure Limits for Electromagnetic Radiation, as Applicable to Smart Meters. Dr. Ron Powell PhD.; 2013

## INDEX TO DEFERRED APPENDIX

139	6700-6705	Jul. 7, 2016	Environmental Health Trust	Smart Meters - Radiation Sickness; Symptoms after Exposure to Smart Meter Radiation. Dr. Ron Powell PhD.; 2015
140	6706-6735	Sep. 3, 2013	Kit Weaver	Kit Weaver, Comments
141	6736-6740	Feb. 6, 2013	Joshua Hart	Organizations - Radiation Sickness; StopSmartMeters, Comments
142 Part 1	6741-6850	Sep. 28, 2016	Kevin Mottus	Cell Phones; Research Abstracts of Over 700 Studies Showing Health Effects from Cell Phone Radio Frequency Radiation; Prof. Henri Lai (Tab 142 Part 1)
<b>VOLUME 18 – Tabs 142 Part 2 - 153</b>				
142 Part 2	6851-7088	Sep. 28, 2016	Kevin Mottus	Cell Phones; Research Abstracts of Over 700 Studies Showing Health Effects from Cell Phone Radio Frequency Radiation; Prof. Henri Lai (Tab 142 Part 2)
143	7089-7099	Sep. 28, 2016	Kevin Mottus	Cancer - Brain Tumors; Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with the use of mobile and cordless phones. Rev Environ Health. (Hardell and Caarlsberg); 2013

## INDEX TO DEFERRED APPENDIX

144	7100-7121	Nov. 18, 2013	Kevin Mottus	Cancer-Brain Tumors; Mobile phone use and brain tumour risk: early warnings, early actions? (Gee, Hardell Carlsberg) (Chapter 21 of Report: “Late lessons from early warnings: science, precaution”); 2013
145	7122-7134	Sep. 12, 2019	Environmental Health Trust	Cell Phones; Real-world cell phone radiofrequency electromagnetic field exposures. Environmental Research. (Wall et al); 2019
146	7135-7142	Nov. 18, 2013	Kevin Mottus	Cancer -Brain Tumors; Meta-analysis of long-term mobile phone use and the association with brain tumours, Prof. Lennart Hardell MD. PhD. 2008
147	7143-7156	Jul. 11, 2016	Environmental Health Trust	Cancer - Brain Tumors; Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. International Journal of Oncology.(Hardell et al); 2013
148	7157-7183	Nov. 18, 2013	Kevin Mottus	Cancer - Brain Tumors; Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology. (Hardell et al); 2012

## INDEX TO DEFERRED APPENDIX

149	7184-7193	Sep. 28, 2016	Kevin Mottus	Cancer - Brain Tumors; Pooled Analysis of Two Swedish Case-Control Studies on the Use of Mobile and Cordless Telephones and the Risk of Brain Tumours Diagnosed During 1997-2003. International Journal of Occupational Safety and Ergonomics (Mild, Hardell, Carlsberg); 2007
150	7194-7210	Dec. 10, 2018	Environmental Health Trust	Thermal and non-thermal health effects of low intensity non-ionizing radiation: An international perspective. Environmental Pollution. (Belpomme et al); 2018
151	7211-7224	Sep. 28, 2016	Kevin Mottus	Cancer - Brain Tumors; Mobile phones, cordless phones and the risk for brain tumours. International Journal of Oncology (Prof. Lennart Hardell MD., PhD.); 2009
152	7225-7251	Sep. 3, 2013	Paul Dart MD	Cancer - Cell Phones; Cell Phones and Risk of Brain Tumor, Dr. Paul Dart MD. (Petitioner); 2013
153	7252-7255	Jan 31, 2019	Julian Gehman	Jullian Gehman Esq. Comments
<b>VOLUME 19 – Tabs 154-168</b>				
154	7256-7371	Nov. 5, 2013	Joel M. Moskowitz Ph.D.	Dr. Joel Moskowitz PhD. Reply Comments, Why the FCC Must Strengthen Radiofrequency Radiation Limits in the U.S.

## INDEX TO DEFERRED APPENDIX

155	7372-7414	Jun. 17, 2014	Environmental Working Group	Cancer - Children; Cell Phone Radiation: Science Review on Cancer Risks and Children's Health; Environmental Working Group; 2009
156	7415-7417	Sep. 30, 2016	Kevin Mottus	Cell Phones - Plants; Review: Weak Radiofrequency Radiation Exposure From Mobile Phone Radiation on Plants. Electromagnetic Biology and Medicine (Malka N. Halgamuge); 2016
157	7418-7421	Apr. 29, 2019	Environmental Health Trust	Testing; Microwave Emissions From Cell Phones Exceed Safety Limits in Europe and the US When Touching the Body. IEEE Access. Prof. Om P. Gandhi PhD.; 2019
158	7422-7426	Sep. 12, 2019	Environmental Health Trust	Testing - Children; Absorption of wireless radiation in the child versus adult brain and eye from cell phone conversation or virtual reality. Environmental Research. (C. Fernandez et al); 2018
159	7427-7431	Jul. 11, 2016	Environmental Health Trust	Yes the Children Are More Exposed to Radiofrequency Energy From Mobile Telephones Than Adults. IEEE Access (Prof. Om Ghandi PhD); 2015
160	7432-7441	Jul. 7, 2016	Environmental Health Trust	Testing - Children; Children Absorb Higher Doses of Radio Frequency Electromagnetic Radiation From Mobile Phones Than Adults. IEEE Access (Robert D. Morris et al); 2015

## INDEX TO DEFERRED APPENDIX

161	7442-7445	Apr. 29, 2019	Environmental Health Trust	Testing – Children; Exposure Limits: The underestimation of absorbed cell phone radiation, especially in children. Electromagnetic Biology and Medicine (Gandhi et al); 2011
162	7446-7504	Nov. 17, 2013	Pong Research Corporation	Testing; Pong Research Corporation Reply Comments
163	7505-7514	Aug. 19, 2012	Pong Research Corporation	Testing; Pong Research Corporation, Letter to the FCC
164	7515-7602	Nov. 17, 2013	L. Lloyd Morgan	Environmental Health Trust, Reply Comments (Erroneous Comments Submitted to the FCC on Proposed Cellphone Radiation Standards and Testing by CTIA – September 3, 2013)
165	7603-7614	Sep. 3, 2013	Dr. Joel M. Moskowitz PhD	“Comments on Notice of Inquiry, ET Docket No. 13-84” GAO Report   “Exposure and Testing Requirements for Mobile Phones Should Be Reassessed.” Dr. Joel Moskowitz PhD.; 2012
166	7615-7628	Sep. 2, 2013	Consumers for Safe Cell Phones	Organizations; Consumers for Safe Cell Phones Comments (Petitioner)
167	7629-7640	Nov. 17, 2013	Consumers for Safe Cell Phones	Consumers for Safe Cell Phone Comments (Reply to CTIA Comments from Sep. 13, 2013)
168	7641-7672	Nov. 17, 2013	Environmental Working Group	Organizations; Environmental Working Group, Reply Comments



## INDEX TO DEFERRED APPENDIX

<b>VOLUME 20 - Tabs 169 – 172 Part 1</b>				
169	7673-7682	Dec. 10, 2018	Environmental Health Trust	Industry Influence; World Health Organization, Radiofrequency Radiation and Health - a Hard Nut to Crack (Review). International Journal of Oncology. Prof. Lennart Hardell MD. PhD.; 2017
170	7683-7716	Nov. 18, 2013	Richard H. Conrad PhD	Industry Influence; Business Bias As Usual: The Case Of Electromagnetic Pollution. Prof. Levis, Prof. Gennaro, Prof. Garbisa
171	7717-7719	Sep. 3, 2013	The EMR Policy Institute	Industry Influence; Prof. Martha Herbert MD PhD., Harvard Pediatric Neurologist Letter to Los Angeles Unified School District; 2013
172 Part 1	7720-8073	Feb. 6, 2013	Dr. Donald R. Maisch PhD	Industry Influence; The Procrustean Approach: Setting Exposure Standards for Telecommunications Frequency Electromagnetic Radiation, Dr. Donald Maisch PhD.; 2009 (Tab 172 Part 1)
<b>VOLUME 21 – Tabs 172 Part 2 - 185</b>				
172 Part 2	8074-8158	Feb. 6, 2013	Dr. Donald R. Maisch PhD	Industry Influence; The Procrustean Approach: Setting Exposure Standards for Telecommunications Frequency Electromagnetic Radiation, Dr. Donald Maisch PhD.; 2009 (Tab 172 Part 2)
173	8159-8167	Sep. 29, 2016	Kevin Mottus	Industry Influence; Illusion and Escape: The Cell Phone Disease Quagmire. Dr. George L. Carlo PhD., JD.; 2008

## INDEX TO DEFERRED APPENDIX

174	8168-8169	Nov. 18, 2013	Kevin Mottus	Industry Influence; Quote of Prof. Henry Lai PhD from NY Times Article about Percent of Negative Studies Funded By Industry; 2013
175	8170-8177	Nov 18, 2013	Kevin Mottus	Industry Influence; Warning: Your Cell Phone May Be Hazardous to Your Health. Christopher Ketcham, GQ; 2010
176	8178-8182	Sep. 3, 2013	Monnie Ramsell	Industry Influence; Radiation Protection in Conflict With Science; Dr. Franz Adlkofer PhD.; 2011
177	8183-8184	Mar. 21, 2019	Office of Engineering and Technology	US Agencies; Letter from the FCC's OET Dept. to Dr. Shuren of the FDA
178	8185-8188	Apr. 30, 2019	Center for Devices and Radiological Health	US Agencies; Letter from Dr. Shuren of the FDA to the FCC's OET Dept.
179	8189-8279	Sep. 24, 2013	Grassroots Environmental Education, Inc.	US Agencies - Radiation Sickness; US Access Board Acknowledgement of Radiation Sickness (Electromagnetic Sensitivities); 2002
180	8280-8377	Sep. 24, 2013	Grassroots Environmental Education, Inc.	US Agencies - Radiation Sickness; National Institute of Building Sciences (NIBS), IEQ Indoor Environmental Quality; Recommendations for Accommodation for Electromagnetic Sensitivity; 2005

## INDEX TO DEFERRED APPENDIX

181	8378-8386	Sep. 29, 2016	Kevin Mottus	US Agencies; US Department of Interior, Letter of the Director of Office of Environmental Policy and Compliance; 2014
182	8387-8407	Mar. 4, 2013	Susan Brinchman, CEP	US Agencies; Department of the Army, Confidential Legal Correspondence, Dec. 13, 2006
183	8408-8411	Sep. 2, 2013	Kevin Mottus	US Agencies; US Environmental Protection Agency (EPA) Letter to EMR Network; Jul. 6, 2002
184	8412-8424	Jul. 7, 2016	Environmental Health Trust	US Agencies; EPA Letter to the FCC, Comments on FCC 93-142 Environmental Effects of RF; 1993
185 Part 1	8425-8505	Jul. 7, 2016	Environmental Health Trust	US Agencies; US Naval Medical Research Institute. Bibliography of Reported Biological Phenomena (“Effects”) and Clinical Manifestations Attributed to Microwave and Radio-frequency Radiation; 1971 (Tab 185 Part 1)
<b>VOLUME 22 – Tabs 185 Part 2 - 238</b>				
185 Part 2	8506-8531	Jul. 7, 2016	Environmental Health Trust	US Agencies; US Naval Medical Research Institute. Bibliography of Reported Biological Phenomena (“Effects”) and Clinical Manifestations Attributed to Microwave and Radio-frequency Radiation; 1971 (Tab 185 Part 2)
186	8532-8636	Jul. 12, 2015	U.S. Department of Labor	US Agencies; US Department of Labor Comment

## INDEX TO DEFERRED APPENDIX

187	8537-8539	Sep. 29, 2016	Kevin Mottus	Radiation Sickness; Exemption for Fire stations, California Assembly Bill No. 57 (2015), codified at Cal. Gov. Code 65964.1
188	8540-8546	Sep. 3, 2013	Susan D. Foster, MSW	Radiation Sickness - Firefighters; Susan Foster Comments
189	8547-8626	Jul. 7, 2016	Environmental Health Trust	Radiation Sickness; Electromagnetic Hypersensitivity, Dr. Erica Mallery-Blythe; 2014
190	8627-8628	Sep. 16, 2019	Joel M. Moskowitz PhD.	Radiation Sickness; Reliable disease biomarkers characterizing and identifying electrohypersensitivity and multiple chemical sensitivity as two etiopathogenic aspects of a unique pathological disorder. Rev Environ Health. (Prof. Belpomme et al); 2015
191	8629-8637	Sep.3, 2013	Kevin Mottus	Radiation Sickness; Electromagnetic hypersensitivity: evidence for a novel neurological syndrome. Int J Neurosci. (McCarty et al); 2011
192	8638-8641	Nov. 18, 2013	Toril H. Jelter MD	Radiation Sickness - Children; Dr. Torill Jelter MD. (Petitioner) Comments
193	8642-8659	Jul. 13, 2016	Deborah Kopald	Radiation Sickness, Deborah Kopald Comments
194	8660-8662	Sep. 30, 2016	Ann Lee MD	Radiation Sickness - Children; Dr. Ann Lee MD. (Petitioner) Comments

## INDEX TO DEFERRED APPENDIX

195	8663-8681	Sep. 3, 2013	Paul Dart MD.	Radiation Sickness; Health Effects of Microwave Radio Exposures. Dr. Paul Dart MD.(Petitioner) Comments
196	8682-8683	Sep. 4, 2013	Erica M. Elliott	Radiation Sickness; Dr. Erica Elliott MD. Comments
197	8684-8734	Sep. 16, 2019	Dr. Joel M. Moskowitz PhD.	Radiation Sickness; Electrohypersensitivity Abstracts; 2017
198	8735-8747	Jul. 11, 2016	Environmental Health Trust	Radiation Sickness; Could Myelin Damage from Radiofrequency Electromagnetic Field Exposure Help Explain the Functional Impairment Electrohypersensitivity? A Review of the Evidence. Journal of Toxicology and Environmental Health. (Redmayne and Johansson); 2014
199	8748-8773	Jul. 11, 2016	Kate Kheel	Radiation Sickness; No Safe Place - shattered lives, healthcare set to crash – you can't fix this fast enough; Letter to a Mayor, Olga Sheean, Jun. 15, 2016
200	8774-8778	Aug. 26, 2013	Sarah Jane Berd	Radiation Sickness; Sarah Jane Berd Comments
201	8779-8782	Feb. 4, 2013	Cynthia S Larson	Radiation Sickness; Cynthia S. Larson Comments
202	8783-8784	Oct. 3, 2016	Josh Fisher	Radiation Sickness; Josh Fisher Comments
203	8785-8787	Oct. 3, 2016	Paul Stanley	Radiation Sickness; Paul Stanley (Petitioner) Comments

## INDEX TO DEFERRED APPENDIX

204	8788-8789	Nov. 25, 2013	Lynnell Rosser	Radiation Sickness; Lynnell Rosser Letter
205	8790-8796	Sep.12, 2013	Charyl Zehfus	Radiation Sickness; Charyl Zehfus Reply Comments
206	8797-8800	Sep. 4, 2013	Annie Starr	Radiation Sickness; Annie Starr Comments
207	8801-8802	Sep. 3, 2013	Rob Bland	Radiation Sickness; Rob Bland Comments
208	8803-8805	Sep. 3, 2013	Nancy Rose Gerler	Radiation Sickness; Nancy Rose Gerler Comments
209	8806-8811	Feb. 5, 2013	Monnie Ramsell	Radiation Sickness; Monnie Ramsell Comments
210	8812-8815	Sep. 3 2013	Miriam D. Weber	Radiation Sickness; Miriam D. Weber Comments
211	8816-8818	Sep. 3 2013	Junghie Elky	Radiation Sickness; Junghie Elky Comments
212	8819-8832	Aug. 30, 2013	Catherine Kleiber	Radiation Sickness; ADA/FHA Catherine Kleiber Comments
213	8833-8837	Sep. 3, 2013	Amanda & Ryan Rose	Radiation Sickness; Amanda & Ryan Rose Comments
214	8838-8842	Sep. 3, 2013	Cindy Bowman	Radiation Sickness; Cindy Bowman Comments
215	8843-8844	Sep. 3, 2013	Sue Martin	Radiation Sickness; Sue Martin Comments
216	8845-8846	Sep. 3, 2013	Richard Gaul	Radiation Sickness; Richard Gaul Comments

## INDEX TO DEFERRED APPENDIX

217	8847-8848	Sep. 4 2013	Karen Strode	Radiation Sickness; Karen Strode Comments
218	8849-8850	Sep. 3, 2013	Jaime Schunkewitz	Radiation Sickness; Jaime Schunkewitz Comments
219	8851-8854	Aug. 13, 2013	Linda Bruce	Radiation Sickness; Linda Bruce Comments
220	8855-8858	Feb. 19, 2013	Louise Kiehl Stanphill	Radiation Sickness; Louise Kiehl Stanphill Reply Comments
221	8859-8862	Feb. 7, 2013	Diana LeRoss	Radiation Sickness; Diana LeRoss Comments, Feb. 7, 2013
222	8863-8866	Jun. 17, 2013	Marc Sanzotta	Radiation Sickness; Marc Sanzotta Comments
223	8867-8868	Aug. 11, 2016	Barbara A. Savoie	Radiation Sickness; Barbara A. Savoie Comments
224	8869-8885	Jul. 13, 2016	R. Kay Clark	Radiation Sickness; R. Kay Clark Comments
225	8886-8887	Sep. 3, 2013	Steve & Juleen Ross	Radiation Sickness; Steve & Juleen Ross Comments
226	8888-8892	Sep. 3, 2013	Kathy Ging	Radiation Sickness; Kathy Ging Comments
227	8893-8895	Sep. 3, 2013	Jeraldine Peterson-Mark	Radiation Sickness; Jeraldine Peterson-Mark Comments
228	8896-8900	Sep. 3, 2013	Edward G.	Radiation Sickness; Edward G. Comments
229	8901-8903	Sep. 4, 2013	D. Yourovski	Radiation Sickness; D. Yourovski Comments

## INDEX TO DEFERRED APPENDIX

230	8904-8907	Sep. 3, 2013	Ellen K. Marks	Radiation Sickness; Ellen K. Marks Comments
231	8908-8911	Sep. 3, 2013	Melody Graves	Radiation Sickness; Melody Graves Comments
232	8912-8913	Sep. 3, 2013	Bernadette Johnston	Radiation Sickness; Bernadette Johnston Comments
233	8914-8916	Sep. 3, 2013	Shane Gregory	Radiation Sickness; Shane Gregory Comments
234	8917-8918	Sep. 3, 2013	Layna Berman	Radiation Sickness; Layna Berman Comments
235	8919-8922	Sep. 3, 2013	Linda Giannoni	Radiation Sickness; Linda Giannoni Comments
236	8923-8925	Sep. 3, 2013	Jennifer Page	Radiation Sickness; Jennifer Page Comments
237	8926-8928	Sep. 3, 2013	Jackie Seward	Radiation Sickness; Jackie Seward Comments
238	8929-8931	Sep. 3, 2013	Elizabeth Feudale	Radiation Sickness; Elizabeth Feudale Comments
<b>VOLUME 23 – Tabs 239-315</b>				
239	8932-8933	Sep. 3, 2013	Brent Dalton	Radiation Sickness; Brent Dalton Comments
240	8934-8937	Sep. 3, 2013	Elizabeth Barris	Radiation Sickness; Elizabeth Barris (Petitioner) Comments
241	8938-8940	Sep. 3, 2013	Olemara	Radiation Sickness; Olemara Comments
242	8941-8943	Aug. 14, 2013	Melissa White	Radiation Sickness; Melissa White Comments



## INDEX TO DEFERRED APPENDIX

243	8944-8946	Jun. 4, 2013	Carol Moore	Radiation Sickness; Carol Moore Comments
244	8947-8952	Mar. 7, 2013	Michele Hertz	Radiation Sickness; Michele Hertz (Petitioner) Comments
245	8953-8955	Mar. 4, 2013	B.J. Arvin	Radiation Sickness; B.J. Arvin Reply Comments
246	8956-8959	Feb. 12, 2013	Suzanne D. Morris	Radiation Sickness; Suzanne D. Morris Comments
247	8960-8962	Feb. 7, 2013	Tom Creed	Radiation Sickness; Tom Creed Comments
248	8963-8967	Feb. 6, 2013	Julie Ostoich	Radiation Sickness; Julie Ostoich Comments
249	8968-8981	Feb. 6, 2013	Kathleen M. Sanchez	Radiation Sickness; Kathleen M. Sanchez Comments
250	8982-8985	Feb. 6, 2013	John Edward Davie	Radiation Sickness; John Edward Davie Comments
251	8986-8989	Feb. 6, 2013	Alison L. Denning	Radiation Sickness; Alison L. Denning Comments
252	8990-9012	Feb. 6, 2013	Susan Brinchman, CEP	Radiation Sickness; Susan Brinchman Comments
253	9013-9016	Feb. 6, 2013	Terilynn Langsev	Radiation Sickness; Terilynn Langsev Comments
254	9017-9020	Feb. 6, 2013	Beth Ann Tomek	Radiation Sickness; Beth Ann Tomek Comments
255	9021-9025	Feb. 5, 2013	Sandra Storwick	Radiation Sickness; Sandra Storwick Comments

## INDEX TO DEFERRED APPENDIX

256	9026-9029	Feb. 5, 2013	Odessa Rae	Radiation Sickness; Odessa Rae Comments
257	9030-9033	Feb. 5, 2013	Kenneth Linoski	Radiation Sickness; Kenneth Linoski Comments
258	9034-9039	Feb. 6, 2013	Elissa Michaud	Radiation Sickness; Elissa Michaud Comments
259	9040-9043	Feb. 5, 2013	Ella Elman	Radiation Sickness; Ella Elman Comments
260	9044-9047	Feb. 5, 2013	Andrew Swerling	Radiation Sickness; Andrew Swerling Comments
261	9048-9051	Feb. 5, 2013	Natalie Smith	Radiation Sickness; Natalie Smith Comments
262	9052-9055	Feb. 4, 2013	Mana Iluna	Radiation Sickness; Mana Iluna Comments
263	9056-9059	Feb. 4, 2013	Jayne G. Cagle	Radiation Sickness; Jayne G. Cagle Comments
264	9060-9063	Feb. 4, 2013	Mark Summerlin	Radiation Sickness; Mark Summerlin Comments
265	9064-9067	Feb. 4, 2013	Lashanda Summerlin	Radiation Sickness; Lashanda Summerlin Comments
266	9068-9071	Feb. 4, 2013	Kath Mason	Radiation Sickness; Kath Mason Comments
267	9072-9084	Nov. 1, 2013	Daniel Kleiber	Radiation Sickness; Daniel Kleiber Reply Comments
268	9085-9086	Sep.3, 2013	Susan MacKay	Radiation Sickness; Susan MacKay Comments

## INDEX TO DEFERRED APPENDIX

269	9087-9091	Mar. 4, 2013	Theresa McCarthy	Radiation Sickness; Theresa McCarthy Reply Comments
270	9092-9093	Jul. 11, 2016	L S Murphy	Radiation Sickness; L S Murphy Comments
271	9094-9096	Aug. 30, 2013	Patricia B. Fiskén	Radiation Sickness; Patricia B. Fiskén Comments
272	9097-9098	Sep. 3, 2013	Linda Hart	Radiation Sickness; Linda Hart Comments
273	9099-9101	Aug. 19, 2013	E Renaud	Radiation Sickness; E Renaud Comments
274	9102-9108	Aug. 13, 2013	Nicole Nevin	Radiation Sickness; Nicole Nevin Comments
275	9109-9110	Sep. 30, 2016	Robert VanEchaute	Radiation Sickness; Robert VanEchaute Comments
276	9111-9112	Sep. 6, 2016	Daniel Berman	Radiation Sickness; Daniel Berman Comments
277	9113-9116	Sep. 3, 2013	Edna Willadsen	Radiation Sickness; Edna Willadsen Comments
278	9117-9118	Aug. 30, 2013	Susan Molloy	Radiation Sickness; Susan Molloy Comments
279	9119-9120	Sep. 3, 2013	Kathleen Christofferson	Radiation Sickness; Kathleen Christofferson Comments
280	9121-9122	Sep. 3, 2013	Juli Johnson	Radiation Sickness; Juli Johnson Comments
281	9123-9124	Sep. 3, 2013	Annalee Lake	Radiation Sickness; Annalee Lake Comments

## INDEX TO DEFERRED APPENDIX

282	9125-9126	Aug. 22, 2013	Alan Marks	Radiation Sickness; Alan Marks Comments
283	9127-9128	Jun. 10, 2013	Peggy McDonald	Radiation Sickness; Peggy McDonald Comments
284	9129-9131	Feb. 26, 2013	Mark Zehfus	Radiation Sickness; Mark Zehfus Reply Comments
285	9132-9137	Feb. 6, 2013	Jennifer Zmarzlik	Radiation Sickness; Jennifer Zmarzlik Comments
286	9138-9142	Feb. 6, 2013	Catherine E. Ryan	Radiation Sickness; Catherine E. Ryan Comments
287	9143-9148	Feb. 6, 2013	L. Meade	Radiation Sickness; L. Meade Comments
288	9149-9150	Sep. 3, 2013	Arthur Firstenberg	Radiation Sickness; Arthur Firstenberg Comments
289	9151-9152	Mar. 5, 2013	Jeromy Johnson	Radiation Sickness; Jeromy Johnson Reply Comments
290	9153-9154	Sep. 26, 2016	Jeanne Insenstein	Radiation Sickness; Jeanne Insenstein Comments
291	9155-9159	Nov. 18, 2013	Angela Flynn	Radiation Sickness; Angela Flynn Reply Comments
292	9160-9162	Sep. 4, 2013	Kathryn K. Wesson	Radiation Sickness; Kathryn K. Wesson Comments
293	9163-9165	Sep. 3, 2013	Diane St. James	Radiation Sickness; Diane St. James Comments
294	9166-9168	Sep. 3, 2013	Christine Hoch	Radiation Sickness; Christine Hoch Comments
295	9169-9180	Sep. 3, 2013	Arlene Ring	Radiation Sickness; Arlene Ring Comments

## INDEX TO DEFERRED APPENDIX

296	9181-9182	Sep. 3, 2013	Victoria Jewett	Radiation Sickness; Victoria Jewett Comments
297	9183-9185	Sep. 3, 2013	Michael J. Hazard	Radiation Sickness; Michael J. Hazard Comments
298	9186-9187	Aug. 30, 2013	Melinda Wilson	Radiation Sickness; Melinda Wilson Comments
299	9188-9191	Aug. 30, 2013	Maggi Garloff	Radiation Sickness; Maggi Garloff Comments
300	9192-9199	Sep. 3, 2013	Holly Manion	Radiation Sickness & ADA/FHA; Holly Manion Comments
301	9200-9203	Aug. 22, 2013	James Baker	Radiation Sickness; James Baker Comments
302	9204-9254	Jul. 19, 2013	Deborah Cooney	Radiation Sickness; Deborah Cooney, Verified Complaint, <i>Cooney v. California Public Utilities Commission et al</i> , No. 12-cv-06466-CW, U.S.D.C. N.D. Cal. (Dec 17, 2012)
303	9255-9258	Jun. 13, 2013	Mardel DeBuhr	Radiation Sickness; Mardel DeBuhr Comments
304	9259-9260	Jun. 10, 2013	Richard Wolfson	Radiation Sickness; Richard Wolfson Comments
305	9261-9264	Mar. 7, 2013	James E. Peden	Radiation Sickness; James E. Peden Reply Comments
306	9265-9266	Mar. 5, 2013	Carl Hilliard	Radiation Sickness; Carl Hilliard Comments
307	9267-9268	Mar. 4, 2013	Lisa Horn	Radiation Sickness; Lisa Horn Comments

## INDEX TO DEFERRED APPENDIX

308	9269-9274	Feb. 27, 2013	Alexandra Ansell	Radiation Sickness; Alexandra Ansell Reply Comments
309	9275-9278	Feb. 25, 2013	Patricia A. Ormsby	Radiation Sickness; Patricia A. Ormsby Reply Comments
310	9279-9282	Feb. 14, 2013	Annette Jewell-Ceder	Radiation Sickness; Annette Jewell-Ceder Reply Comments
311	9283-9286	Feb. 6, 2013	Max Feingold	Radiation Sickness; Max Feingold Comments
312	9287-9300	Feb. 6, 2013	Annallys Goodwin-Landher	Radiation Sickness; Annallys Goodwin-Landher Comments
313	9301-9316	Feb. 4, 2013	Rebecca Morr	Radiation Sickness; Rebecca Morr Comments
314	9317-9320	Feb. 5, 2013	Josh Finley	Radiation Sickness; Alexandra Ansell Reply Comments
315	9321-9331	Feb. 5, 2013	Donna L. Bervinchak	Radiation Sickness; Donna L. Bervinchak Comments
<b>VOLUME 24 – Tabs 316-377</b>				
316	9332-9334	Feb. 5, 2013	Catherine Morgan	Radiation Sickness; Catherine Morgan Comments
317	9335-9338	Feb. 5, 2013	Angelica Rose	Radiation Sickness; Angelica Rose Comments
318	9339-9341	Feb. 5, 2013	Brian J. Bender	Radiation Sickness; Brian J. Bender Comments
319	9342-9343	Jul. 11, 2016	Maggie Connolly	Radiation Sickness; Maggie Connolly Comments

## INDEX TO DEFERRED APPENDIX

320	9344-9345	Sep. 3, 2013	Gregory Temmer	Radiation Sickness; Gregory Temmer Comments
321	9346-9347	Sep. 3, 2013	Bernice Nathanson	Radiation Sickness; Bernice Nathanson Comments
322	9348-9350	Sep. 3, 2013	Terry Losansky	Radiation Sickness; Terry Losansky Comments
323	9351-9352	Sep. 3, 2013	Ronald Jorstad	Radiation Sickness; Ronald Jorstad Comments
324	9353-9354	Jul. 8, 2013	Liz Menkes	Radiation Sickness; Liz Menkes Comments
325	9355-9356	Sep. 3, 2013	Katie Mickey	Radiation Sickness; Katie Mickey Comments
326	9357-9360	Sep. 3, 2013	Karen Nold	Radiation Sickness; Karen Nold Comments
327	9361-9362	Jul. 8, 2013	David DeBus, PhD.	Radiation Sickness; David DeBus, Ph.D. Comments
328	9363-9365	Jun. 20, 2013	Jamie Lehman	Radiation Sickness; Jamie Lehman Comments
329	9366-9367	Jun. 12, 2013	Jane van Tamelen	Radiation Sickness; Jane van Tamelen Comments
330	9368-9379	Jun. 10, 2013	Sebastian Sanzotta	Radiation Sickness; Sebastian Sanzotta Comments
331	9380-9383	Mar. 7, 2013	Taale Laafi Rosellini	Radiation Sickness; Taale Laafi Rosellini Reply Comments
332	9384-9387	Mar. 7, 2013	Robert E. Peden	Radiation Sickness; Robert E. Peden Reply Comments

## INDEX TO DEFERRED APPENDIX

333	9388-9391	Mar. 7, 2013	Marilyn L. Peden	Radiation Sickness; Marilyn L. Peden Reply Comments
334	9392-9393	Mar. 5, 2013	Doreen Almeida	Radiation Sickness; Doreen Almeida Reply Comments
335	9394-9395	Mar. 5, 2013	Oriannah Paul	Radiation Sickness; Oriannah Paul Comments
336	9396-9397	Sep. 3, 2013	Heather Lane	Radiation Sickness; Heather Lane Comments
337	9398-9399	Aug. 15, 2013	John Grieco	Radiation Sickness; John Grieco Comments
338	9400-9401	Sep. 29, 2016	Linda Kurtz	Radiation Sickness & ADA/FHA; Linda Kurtz Comments
339	9402-9406	Feb. 5, 2013	Lisa Drodt-Hemmele	Radiation Sickness & ADA/FHA; Lisa Drodt-Hemmele Comments
340	9407-9409	Aug. 26, 2013	Robert S Weinhold	Radiation Sickness & ADA/FHA; Robert S Weinhold Comments
341	9410-9411	Jul. 12, 2016	Dianne Black	Radiation Sickness & ADA/FHA; Dianne Black Comments
342	9412-9415	Jul. 13, 2016	Derek C. Bishop	Radiation Sickness & ADA/FHA; Derek C. Bishop Comments
343	9416-9435	Aug. 21, 2013	Steven Magee	Radiation Sickness & ADA/FHA; Steven Magee Comments
344	9436-9437	Sep. 3, 2013	Melissa Chalmers	Radiation Sickness & ADA/FHA; Melissa Chalmers Comments



## INDEX TO DEFERRED APPENDIX

345	9438-9440	Aug. 30, 2013	Garril Page	Radiation Sickness & ADA/FHA; Garril Page Comments
346	9441-9444	Sep. 5, 2013	Laddie W. Lawings	Radiation Sickness & ADA/FHA; Laddie W. Lawings Comments
347	9445-9446	Sep. 4, 2018	Fern Damour	Radiation Sickness & ADA/FHA; Fern Damour Comments
348	9447-9449	Aug. 28, 2013	Rebecca Rundquist	Radiation Sickness & ADA/FHA; Rebecca Rundquist Comments
349	9450-9451	Sep. 3, 2013	JoAnn Gladson	Radiation Sickness & ADA/FHA; JoAnn Gladson Comments
350	9452-9453	Jul. 13, 2016	Jonathan Mirin	Radiation Sickness & ADA/FHA; Jonathan Mirin Comments
351	9454-9455	Jul. 12, 2016	Mary Adkins	Radiation Sickness & ADA/FHA; Mary Adkins Comments
352	9456-9458	Sep. 3, 2013	Ian Greenberg	Radiation Sickness & ADA/FHA; Ian Greenberg Comments
353	9459-9462	Sep. 3, 2013	Helen Sears	Radiation Sickness & ADA/FHA; Helen Sears Comments
354	9463-9464	Mar. 4, 2013	Janet Johnson	Radiation Sickness & ADA/FHA; Janet Johnson Comments
355	9465-9467	Aug. 20, 2013	Mr. and Mrs. Gammone	Radiation Sickness & ADA/FHA; Mr. and Mrs. Gammone Comments
356	9468-9475	Sep. 10, 2013	Shelley Masters	Radiation Sickness - Disability; Shelley Masters Comments

## INDEX TO DEFERRED APPENDIX

357	9476-9479	Sep. 12, 2016	Tara Schell & Kathleen Bowman	Radiation Sickness; Disability; Tara Schell & Kathleen Bowman Comments
358	9480-9481	Feb. 6, 2013	Patricia Burke	Radiation Sickness; Disability; Patricia Burke Comments
359	9482-9484	Aug. 19, 2013	Deirdre Mazzetto	Radiation Sickness; Disability; Deirdre Mazzetto Comments
360	9485-9486	Mar. 5, 2013	Jim and Jana May	Radiation Sickness; Disability; Jim and Jana May Comments
361	9487-9488	Jun. 10, 2013	Lisa M. Stakes	Radiation Sickness; Disability; Lisa M. Stakes Comments
362	9489-9490	Sep. 3, 2013	Veronica Zrnchik	Radiation Sickness; Disability; Veronica Zrnchik Comments
363	9491-9493	Sep. 12, 2013	J.A. Wood	Radiation Sickness; Disability; J.A. Wood Comments
364	9494-9495	Jul. 3, 2016	Sherry Lamb	Radiation Sickness; Disability; Sherry Lamb Comments
365	9496-9500	Aug. 28, 2013	April Rundquist	Radiation Sickness; Disability; April Rundquist Comments
366	9501-9502	Jul. 21, 2016	Charlene Bontrager	Radiation Sickness; Disability; Charlene Bontrager Comments
367	9503-9506	Jun. 19, 2013	Michelle Miller	Radiation Sickness; Disability; Michelle Miller Comments

## INDEX TO DEFERRED APPENDIX

368	9507-9514	Sep. 3, 2013	James C. Barton	Radiation Sickness; Disability; James C. Barton Comments
369	9515-9526	Sep. 3, 2013	Diane Schou	Radiation Sickness; Disability; Diane Schou Comments
370	9527-9532	Jun. 24, 2013	Alison Price	Radiation Sickness; Disability; Alison Price Comments
371	9533-9535	Sep. 10, 2013	Shari Anker	Radiation Sickness; Disability; Shari Anker Comments
372	9536-9538	Aug. 30, 2013	Paul Vonharnish	Radiation Sickness; Disability; Paul Vonharnish Comments
373	9539-9548	Aug. 26, 2013	Heidi Lumpkin	Radiation Sickness; Disability; Heidi F. Lumpkin, Comments
374	9549-9550	Sep. 3, 2013	Kaitlin Losansky	Radiation Sickness; Disability; Kaitlin Losansky Comments
376	9551-9556	Nov. 12, 2012	Monise Sheehan	Radiation Sickness; Disability; Monise Sheehan Testimonial
376	9557-9558	Mar. 1, 2013	Ruthie Glavinich	Radiation Sickness; Disability; Ruthie Glavinich Comments
377	9559-9682	Sep. 3, 2013	Ed Friedman	Radiation Sickness; Testimonials of Nine People; 2013
<b>VOLUME 25 – Tabs 378-404</b>				
378	9683-9771	Sep. 3, 2013	Ed Friedman	Radiation Sickness; Testimonials of Twelve People; 2013
379	9772-9854	Sep. 3, 2013	Ed Friedman	Radiation Sickness; Testimonials of Nine People; 2013

## INDEX TO DEFERRED APPENDIX

380	9855-9936	Sep. 28, 2016	Kevin Mottus	Radiation Sickness; Testimonials of Twenty People, Collected by StopSmartMeters; 2013
381	9937-9938	Sep. 3, 2013	Amanda & Ryan Rose	Radiation Sickness: Doctor's Diagnosis Letter for Peter Rose; 2010
382	9939-9940	Jun. 10, 2013	Steven Magee	Radiation Sickness; Doctor's Diagnosis Letter for Steven Magee
383	9941-9964	Sep. 30, 2016	Patricia Burke	European Manifesto in support of a European Citizens' Initiative (ECI)
384	9965-10012	Jul. 7, 2016	Environmental Health Trust	ADA/FHA; Verified Complaint, <i>G v. Fay Sch., Inc.</i> , No. 15-CV-40116-TSH (U.S.D.C. Mass. Aug. 12, 2015)
385	10013-10015	Aug. 13, 2013	John Puccetti	ADA/FHA; Organizations; American Academy of Environmental Medicine, Letter to the FCC
386	10016-10018	Feb. 5, 2013	Rachel Nummer	ADA/FHA; Rachel Nummer Comments
387	10019-10023	Feb. 5, 2013	Barbara Schnier	ADA/FHA; Southern Californians for a Wired Solution to Smart Meters Comments
388	10024-10057-	Feb. 5, 2013	Barbara Schnier	ADA/FHA; Opening Brief of Southern Californians for Wired Solutions to Smart Meters, Application 11-03-014 (July 19, 2012)
389	10058-10066	Sep. 2, 2013	Barbara Li Santi	ADA/FHA; Barbara Li Santi Comments
390	10067-10077	Oct. 22, 2013	Kit T. Weaver	ADA/FHA; Kit T. Weaver, Reply Comments

## INDEX TO DEFERRED APPENDIX

391	10078-10086	Mar. 3, 2013	Sandra Schmidt	ADA/FHA; Sandra Schmidt Reply Comments
392	10087-10099	Feb. 11, 2013	Antoinette Stein	ADA/FHA; Antoinette Stein Comments
393	10100-10103	Feb. 5, 2013	David Morrison	ADA/FHA; David Morrison Comments
394	10104-10107	Apr. 16, 2014	MK Hickox	MK Hickox Reply Comments
395	10108-10009	Sep. 3, 2013	Annemarie Weibel	ADA/FHA; Annemarie Weibel Comments
396	10110 - 10117	Sep. 3, 2013	Omer Abid, MD, MPH	Individual Rights; Dr. Omer Abid MD. MPH Comments
397	10118-10120	Sep. 2, 2013	John A. Holeton	Individual Rights; John & Pauline Holeton Comments
398	10121-10129	Sep. 2, 2013	Grassroots Environmental Education, Inc. o/b/o Nancy Naylor	Individual Rights; Nancy Naylor Comments
399	10130-10143	Sep. 2, 2013	Deborah M. Rubin	Individual Rights; Deborah M. Rubin Comments
400	10,144-10149	Sep. 2, 2013	Kevin Mottus	Individual Rights; Kevin Mottus Comments
401	10150 - 10157	Aug. 30, 2013	Alexandra Ansell	Individual Rights; Alexandra Ansell Comments
402	10158-10161	Aug. 25, 2013	Steen Hviid	Individual Rights; Steen Hviid Comments
403	10162-10165	Aug. 21, 2013	Molly Hauck	Individual Rights; Molly Hauck Comments

## INDEX TO DEFERRED APPENDIX

404	10166-10171	Feb. 5, 2013	Olle Johansson	Individual Rights; Prof. Olle Johansson PhD., Comments
<b>VOLUME 26 – Tabs 405-443</b>				
405	10172-10174	Mar. 4, 2013	R.Paul and Kathleen Sundmark	Individual Rights; R. Paul and Kathleen Sundmark Reply Comments
406	10175-10180	Feb. 5, 2013	Cynthia Edwards	Individual Rights & ADA; Cynthia Edwards Comments
407	10181-10185	Feb. 4, 2013	Diana Ostermann	Individual Rights; Diana Ostermann Comments
408	10186-10193	Jul. 13, 2016	Chris Nubbe	Individual Rights; Chris Nubbe Comments
409	10194-10201	Nov. 17, 2013	Katie Singer	Individual Rights & ADA; Katie Singer Comments
410	10202-10203	Aug. 21, 2013	John Puccetti	Individual Rights; BC Human Rights Tribunal approves smart meter class action, Citizens for Safe Technology
411	10204-10207	Sep. 30, 2016	Catherine Kleiber	Individual Rights; Wireless Technology Violates Human Rights, Catherine Kleiber
412	10208-10212	Oct. 28, 2013	Kate Reese Hurd	Individual Rights; Kate Reese Hurd Comments
413	10213-10214	Sep. 30, 2016	Patricia Burke	Individual Rights; Wireless ““Revolution” Must Be Supported by Scientific Proof of Safety for Human Health and the Environment, Patricia Burke

## INDEX TO DEFERRED APPENDIX

414	10215-10216	Sep. 3, 2013	Ed Friedman	Individual Rights; Transcript of Hearing, Vol. 10, Application 11-03-014, Application of Pacific Gas and Electric Company for Approval of Modifications to its SmartMeter™ Program and Increased Revenue Requirements to Recover the Costs of the Modifications, California Public Utilities Commission; Dec. 20, 2012
415	10235-10248	Dec. 1, 2013	Julienne Battalia	Individual Rights; Letter of Complaint and Appeal, and Notice of Liability Regarding ‘Smart Meter’ and Wireless Networks, Julienne Battalia, Washington State
416	10249-10270	Jul. 7, 2016	Environmental Health Trust	Precautionary Principle; Mobile Phone Infrastructure Regulation in Europe: Scientific Challenges and Human Rights Protection, Professor Susan Perry, (international human rights law) Professor Claudia Roda (Impacts of digital technology on human behavior and social structure)
417	10271-10275	Jul. 11, 2016	Environmental Health Trust	Precautionary Principle; Wi-Fi - Children; Saying Good-Bye to WiFi A Waldorf School Takes a Precautionary Step, Dr. Ronald E. Koetzsch PhD.

## INDEX TO DEFERRED APPENDIX

418	10276-10290	Jul. 7, 2016	Environmental Health Trust	Precautionary Principle; Wireless Devices, Standards, and Microwave Radiation in the Education Environment, Dr. Gary Brown, Ed.D. (Instructional Technologies and Distance Education)
419	10291-10294	Nov. 18, 2013	Richard H. Conrad, Ph.D.	Precautionary Principle; Dr. Richard H. Conrad Reply Comments
420	10295-10304	Sep. 3, 2013	Holly Manion	Precautionary Principle; Smart Meters-Firefighters; Letter from Susan Foster to San Diego Gas & Electric, California Public Utilities Commission; Nov. 8, 2011
421	10305-10348	Jul. 7, 2016	Environmental Health Trust	Precautionary Principle; Letter to the Montgomery County Board of Education Members, Theodora Scarato
422	10349-10352	Oct. 30, 2013	Diane Hickey	Precautionary Principle; Diane Hickey Comments
423	10353-10356	Sep. 3, 2013	Monnie Ramsell	Precautionary Principle; Monnie Ramsell Comments
424	10357-10409	Aug. 29, 2013	Kevin Kunze	Precautionary Principle; Kevin Kunze Comments
425	10410-10429	Feb. 6, 2013	Clara De La Torre	Precautionary Principle; Clara de La Torre Comments
426	10430-10431	Sep. 30, 2016	Center for Safer Wireless	Precautionary Principle; Center for Safer Wireless Comments



## INDEX TO DEFERRED APPENDIX

427	10432-10440	Sep. 27, 2016	Gary C. Vesperman	Precautionary Principle; Possible Hazards of Cell Phones and Towers, Wi-Fi, Smart Meters, and Wireless Computers, Printers, Laptops, Mice, Keyboards, and Routers Book Three, Gary Vesperman Comments
428	10441-10443	Jul. 11, 2016	Cecelia Doucette	Precautionary Principle; Cecelia Doucette Comments
429	10444-10446	Aug. 31, 2016	Chuck Matzker	Precautionary Principle; Chuck Matzker Comments
430	10447-10460	Sep. 3, 2013	Diane Schou	Precautionary Principle; Dr. Diane Schou PhD, Dr. Bert Schou, PhD., Comments (letter sent to FCC's OET)
431	10461-10465	Sep. 3, 2013	Evelyn Savarin	Precautionary Principle; Evelyn Savarin Comments
432	10466-10468	Jun. 19, 2013	Jamie Lehman	Precautionary Principle; Jamie Lehman, Comments
433	10469-10470	Mar. 7, 2013	Marlene Brenhouse	Precautionary Principle; Marlene Brenhouse, Comments
434	10471-10474	Jul. 11, 2016	Lynn Beiber	Precautionary Principle; Lynn Beiber Comments
435	10475-10489	Sep. 2, 2013	Kevin Mottus	Precautionary Principle; Kevin Mottus Comments
436	10490-10491	Jul.13, 2016	Mary Paul	Precautionary Principle; Mary Paul, Comments
437	10492-10493	Jul. 11, 2016	Stephanie McCarter	Precautionary Principle; Stephanie McCarter Comments

## INDEX TO DEFERRED APPENDIX

438	10494-10496	Feb. 4, 2013	Rebecca Morr	Precautionary Principle; Rebecca Morr Comments
439	10497-10505	Feb. 3, 2013	Nancy Baer	Precautionary Principle; Nancy Baer Comments
440	10506-10507	Sep. 2, 2013	Holly LeGros	Precautionary Principle; Holly LeGros Comments
441	10508-10509	Aug. 18, 2013	Loe Griffith	Precautionary Principle; Loe Griffith Comments
442	10510-10555	Nov. 18, 2013	EMR Policy Institute	EMR Policy Institute Reply Comments
443	10566-10572	Sep. 3, 2013	Leslee Cooper	Leslee Cooper Comments

Mechanisms of Harm; Meta-Analysis, Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn Biol Med (Yakymenko et al).; 2016

## REVIEW ARTICLE

## Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation

Igor Yakymenko<sup>1</sup>, Olexandr Tsybulin<sup>2</sup>, Evgeniy Sidorik<sup>1</sup>, Diane Henshel<sup>3</sup>, Olga Kyrylenko<sup>4</sup> and Sergiy Kyrylenko<sup>5</sup>

<sup>1</sup>Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine, Kyiv, Ukraine, <sup>2</sup>Department of Biophysics, Bila Tserkva National Agrarian University, Bila Tserkva, Ukraine, <sup>3</sup>School of Public and Environmental Affairs, Indiana University Bloomington, Bloomington, IN, USA, <sup>4</sup>A.I.Virtanen Institute, University of Eastern Finland, Kuopio, Finland, and <sup>5</sup>Department of Structural and Functional Biology, University of Campinas, Campinas, SP, Brazil

## Abstract

This review aims to cover experimental data on oxidative effects of low-intensity radiofrequency radiation (RFR) in living cells. Analysis of the currently available peer-reviewed scientific literature reveals molecular effects induced by low-intensity RFR in living cells; this includes significant activation of key pathways generating reactive oxygen species (ROS), activation of peroxidation, oxidative damage of DNA and changes in the activity of antioxidant enzymes. It indicates that among 100 currently available peer-reviewed studies dealing with oxidative effects of low-intensity RFR, in general, 93 confirmed that RFR induces oxidative effects in biological systems. A wide pathogenic potential of the induced ROS and their involvement in cell signaling pathways explains a range of biological/health effects of low-intensity RFR, which include both cancer and non-cancer pathologies. In conclusion, our analysis demonstrates that low-intensity RFR is an expressive oxidative agent for living cells with a high pathogenic potential and that the oxidative stress induced by RFR exposure should be recognized as one of the primary mechanisms of the biological activity of this kind of radiation.

## Keywords

Cellular signaling, cancer, free radicals, oxidative stress, radiofrequency radiation, reactive oxygen species

## History

Received 10 January 2015

Accepted 12 April 2015

Published online 7 July 2015

## Introduction

Intensive development of wireless technologies during the last decades led to a dramatic increase of background radiofrequency radiation (RFR) in the human environment. Thus, the level of indoor background RFR in industrialized countries increased 5,000-fold from 1985 to 2005 (Maes, 2005). Such significant environmental changes may have a serious impact on human biology and health. As a proof of such impact, a series of epidemiological studies on the increased risk of tumorigenesis in “heavy” users of wireless telephony exists (Hardell et al., 2007, 2011; Sadetzki et al., 2008; Sato et al., 2011). Some studies indicate that long-term RFR exposure in humans can cause various non-cancer disorders, e.g., headache, fatigue, depression, tinnitus, skin irritation, hormonal disorders and other conditions (Abdel-Rassoul et al., 2007; Buchner & Eger, 2011; Chu et al., 2011; Johansson, 2006; Santini et al., 2002; Yakymenko et al., 2011). In addition, convincing studies on hazardous effects of RFR in human germ cells have been published (Agarwal et al., 2009; De Iuliis et al., 2009).

All abovementioned studies dealt with the effects of low-intensity RFR. This means that the intensity of radiation was far below observable thermal effects in biological tissues, and far below safety limits of the International Commissions on Non-Ionizing Radiation Protection (ICNIRP) (ICNIRP, 1998). To date, molecular mechanisms of non-thermal effects of RFR are still a bottleneck in the research on the biological/health effects of low-intensity RFR, although recently many studies have been carried out on metabolic changes in living cells under low-intensity RFR, and comprehensive reviews were published (Belyaev, 2010; Consales et al., 2012; Desai et al., 2009; Yakymenko et al., 2011). In the present work, we analyze the results of molecular effects of low-intensity RFR in living cells and model systems, with a special emphasis on oxidative effects and free radical mechanisms. It might seem paradoxical that, despite being non-ionizing, RFR can induce significant activation of free radical processes and overproduction of reactive oxygen species (ROS) in living cells. We believe that the analysis of recent findings will allow recognition of a general picture of the potential health effects of already ubiquitous and ever-increasing RFR.

## Radiofrequency radiation

RFR is a part of electromagnetic spectrum with frequencies from 30 kHz to 300 GHz. RFR is classified as non-ionizing,

Address correspondence to Prof. Igor Yakymenko, Laboratory of Biophysics, Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine, Vasylykivska str. 45, Kyiv, 03022 Ukraine. E-mail: iyakymen@gmail.com

which means that it does not carry sufficient energy for ionization of atoms and molecules. A part of RFR with the highest frequencies (300 MHz to 300 GHz) is referred to as microwaves (MWs). MW is RFR with the highest energy, which can potentially generate the highest thermal effects in the absorbing matter.

The main indexes of RFR are (i) frequency (Hz); (ii) intensity or power density (PD) of radiation ( $\text{W/m}^2$  or  $\mu\text{W/cm}^2$ ); (iii) its modulated or non-modulated nature; and (iv) continuous or discontinuous pattern of radiation. For the absorbed RFR energy, a parameter of specific absorption rate (SAR) is used ( $\text{W/kg}$ ). The most common digital standard of RFR for mobile communication is still GSM (Global System for Mobile communication), which utilizes frequencies at about 850, 900, 1800 and 1900 MHz. This radiation is frequency modulated, with channel rotation frequency of 217 Hz, and belongs to the radiation of the pulsed mode (Hyland, 2000).

As to the international safety limits, the ICNIRP recommendations restrict intensity of RFR to 450–1000  $\mu\text{W/cm}^2$  (depending on the frequency of radiation) and the SAR value to 2  $\text{W/kg}$ , as calculated for human heads and torsos (ICNIRP, 1998). These indexes were adopted by ICNIRP based on the behavioral response of laboratory rats, which were exposed to gradually increased intensities of RFR to determine the point at which the animals became thermally distressed (Gandhi et al., 2012).

Low-intensity RFR is referred to as radiation with intensities which do not induce significant thermal effects in biological tissues. Accordingly, any intensity of RFR under the ICNIRP limits can be referred to as low-intensity. In this paper we will analyze only the effects of low-intensity RFR.

### Physical/biophysical effects of low-intensity RFR in living cells

RFR, especially MW, can produce thermal effects in matter due to interaction with charged particles, including free electrons, ions or polar molecules, inducing their oscillations in electromagnetic field. The thermal effect of MW can be seen when warming food in the microwave. The effect strongly depends on the intensity of radiation and is mostly negligible under low-intensity RFR conditions. On the other hand, energy of RFR/MW is insufficient not only for the ionization of molecules, but even for activation of orbital electrons. Hence, RFR was often assessed as a factor producing only thermal effects. Nevertheless, evident biological effects of low-intensity RFR promoted research on physical mechanisms of non-thermal biological effects of this kind of radiation.

A biophysical model of a forced-vibration of free ions on the surface of a cell membrane due to external oscillating electromagnetic field (EMF) was proposed (Panagopoulos et al., 2000, 2002). According to the authors, this vibration of electric charges can cause disruption of the cellular electrochemical balance and functions.

A “moving charge interaction” model was proposed for low-frequency EMF (Blank and Soo, 2001). The authors explained activation of genes and synthesis of stress proteins under EMF exposure due to interaction of the field with moving electrons in DNA (Blank and Soo, 2001; Goodman and Blank, 2002). They also demonstrated that EMF

increased electron transfer rates in cytochrome oxidase and accelerated charges in the Na,K-ATPase reaction. Moreover, they demonstrated acceleration of the oscillating Belousov–Zhabotinski reaction in homogeneous solutions due to the application of low-frequency EMF (Blank and Soo, 2003).

An ability of low-strength magnetic fields to trigger onset and offset-evoked potentials was demonstrated (Marino et al., 2009). Effectiveness of a rapid magnetic stimulus (0.2 ms) has led the authors to a conclusion on direct interaction between the field and ion channels in plasma membrane. A plausible mechanism of overproduction of free radicals in living cell due to electron spin flipping in confined free radical pairs in magnetic field of RFR was proposed (Georgiou, 2010).

A significant effect of low-intensity RFR on ferritin, an iron cage protein present in most living organisms from bacteria to humans, was revealed (Céspedes and Ueno, 2009). Exposure of ferritin solution to low-intensity RFR significantly, up to threefold, reduced iron chelation with ferrozine. The authors explained that magnetic field of RFR plays a principle role in the observed effect, and that this effect is strongly non-thermal. The non-thermal mechanism of the interaction of RFR magnetic fields with ferritin is supposedly mediated by an inner super-paramagnetic nanoparticle ( $9\text{H}_2\text{O} \times 5\text{Fe}_2\text{O}_3$  with up to 4500 iron ions), which is a natural phenomenon intrinsic to the cells. It results in reduction of input of iron chelates into the ferritin cage. The authors underlined the potential role of ferritin malfunction for oxidative processes in living cell due to the participation of  $\text{Fe}^{2+}$  ions in the Fenton reaction, which produces hydroxyl radicals. In this respect, it is interesting to point to the results of an *in vitro* study with RFR exposure of rat lymphocytes treated by iron ions (Zmysłony et al., 2004). Although RFR exposure (930 MHz) did not induce detectable intracellular ROS overproduction, the same exposure in the presence of  $\text{FeCl}_2$  in the lymphocyte suspensions induced a significant overproduction of ROS.

Another set of studies indicates on a possibility of changes in protein conformation under RFR exposure. Thus, low-intensity 2.45 MHz RFR accelerated conformational changes in  $\beta$ -lactoglobulin through excitation of so-called collective intrinsic modes in the protein (Bohr and Bohr, 2000a, 2000b), which suggests a principal ability of RFR to modulate the non-random collective movements of entire protein domains. Similarly, a frequency-dependent effect on intrinsic flexibility in insulin structure due to applied oscillating electric field was demonstrated (Budi et al., 2007). Moreover, macromolecular structure of cytoskeleton was significantly altered in fibroblasts of Chinese hamster after the exposure to modulated RFR of the GSM standard (Pavicic and Trosic, 2010). Thus, a 3 h exposure of fibroblasts to modulated RFR (975 MHz) led to significant changes in the structure of microtubules and actin microfilaments, which have polar cytoskeleton structures, while non-polar vimentin filaments reportedly stayed unchanged. Taking into account an extensive regulatory potential of cytoskeleton on cell homeostasis, these data could obviously add to the nature of the biological effects of RFR.

It was shown that ornithine decarboxylase (ODC) can significantly change its activity under low-intensity RFR exposure (Byus et al., 1988; Hoyto et al., 2007; Litovitz et al., 1993, 1997; Paulraj et al., 1999).

In addition, so-called “calcium effects” under RFR exposure in living cells have been demonstrated (Dutta et al., 1989; Paulraj et al., 1999; Rao et al., 2008), which include a significant increase in intracellular  $\text{Ca}^{2+}$  spiking. Taking into account that calcium is a ubiquitous regulator of cellular metabolism, these data point to a possibility that non-thermal RFR can activate multiple  $\text{Ca}^{2+}$ -dependent signaling cascades.

Finally, an ability of low-intensity MW to dissociate water molecules was demonstrated in model experiments years ago (Vaks et al., 1994). In these experiments, MW of 10 GHz with radiated power 30 mW produced a significant level of  $\text{H}_2\text{O}_2$  in deionized water (and also in  $\text{MgSO}_4$  solution) under stable temperature conditions. According to the authors, a kinetic excitation of liquid water associates  $\text{C}(\text{H}_2\text{O})$  upon the absorption of MW leads to subsequent viscous losses due to friction between moving clusters of water molecules. It results in partial irreversible decomposition of water, including breaks of intramolecular bonds ( $\text{H}-\text{OH}$ ) due to a mechanochemical reaction, and generation of  $\text{H}^\bullet$ ;  $\text{OH}^\bullet$ ;  $\text{H}^+$  and  $\text{OH}^-$  groups. Among these, the hydroxyl radical ( $\text{OH}^\bullet$ ) is the most aggressive form of ROS, which can break any chemical bond in surrounding molecules (Halliwell, 2007). The authors assessed that this type of mechanochemical transformation in water could be responsible for  $10^{-4}$ – $10^{-8}$  relative parts of the total MW energy absorbed. Given the fact that the water molecules are ubiquitous in living cells, even a subtle chance for dissociation of water molecules under low-intensity RFR exposure could have a profound effect on tissue homeostasis. It is of note here that one  $\text{OH}^\bullet$  radical can initiate irreversible peroxidation of many hundreds of macromolecules, e.g. lipid molecules (Halliwell, 1991). Taken together, these data show that non-thermal RFR can be absorbed by particular charges, molecules and cellular structures, and in this way can potentially induce substantial modulatory effects in living cell.

### Generation of reactive oxygen species under RFR exposure in living cells

NADH oxidase of cellular membrane was suggested as a primary mediator of RFR interaction with living cells (Friedman et al., 2007). Using purified membranes from HeLa cells, the authors experimentally proved that the exposure to RFR of 875 MHz,  $200 \mu\text{W}/\text{cm}^2$  for 5 or 10 min significantly, almost threefold, increased the activity of NADH oxidase. NADH oxidases are membrane-associated enzymes that catalyze one-electron reduction of oxygen into superoxide radical using NADH as a donor of electron, thus producing powerful ROS. This enzyme has been traditionally known due to its role in induction of oxidative burst in phagocytes as a part of immune response. Yet, later the existence of non-phagocytic NAD(P)H oxidases was revealed in various types of cells, including fibroblasts, vascular and cardiac cells (Griendling et al., 2000). Obviously, the presence of superoxide-generating enzyme in many types of non-phagocytic cells points to the considerable regulatory roles of ROS in living cells. On the other hand, an ability of low-intensity RFR to modulate the activity of the NADH oxidase automatically makes this

factor a notable and potentially dangerous effector of cell metabolism. Notably, the authors pointed out that the acceptor of RFR is different from the peroxide-generating NADPH oxidases, which are also found in plasma membranes (Low et al., 2012).

The other powerful source of ROS in cells is mitochondrial electron transport chain (ETC), which can generate superoxide due to breakdowns in electron transport (Inoue et al., 2003). It was demonstrated that generation of ROS by mitochondrial pathway can be activated under RFR exposure in human spermatozoa (De Iuliis et al., 2009). The authors revealed a dose-dependent effect of 1.8 GHz RFR exposure on ROS production in spermatozoa, particularly in their mitochondria. The significantly increased level of total ROS in spermatozoa was detected under RFR with  $\text{SAR} = 1 \text{ W/kg}$ , which is below the safety limits accepted in many countries. It was demonstrated recently in our laboratory that the exposure of quail embryos *in ovo* to extremely low-intensity RFR (GSM 900 MHz,  $0.25 \mu\text{W}/\text{cm}^2$ ) during the initial days of embryogenesis resulted in a robust overproduction of superoxide and nitrogen oxide radicals in mitochondria of embryonic cells (Burlaka et al., 2013). It is not clear yet which particular part of ETC is responsible for the interaction with RFR. To date, three possible sites of generation of superoxide in ETC have been shown: the ETC complex I (Inoue et al., 2003), complex II (Liu et al., 2002), and complex III (Guzy and Schumacker, 2006). A significant inverse correlation between mitochondrial membrane potential and ROS levels in living cell was found (Wang et al., 2003). As the authors underlined, such a relationship could be due to two mutually interconnected phenomena: ROS causing damage to the mitochondrial membrane, and the damaged mitochondrial membrane causing increased ROS production.

In addition to the well-established role of the mitochondria in energy metabolism, regulation of cell death is a second major function of these organelles. This, in turn, is linked to their role as the powerful intracellular source of ROS. Mitochondria-generated ROS play an important role in the release of cytochrome c and other pro-apoptotic proteins, which can trigger caspase activation and apoptosis (Ott et al., 2007). A few reports indicate on activation of apoptosis due to low-intensity RFR exposure. In human epidermoid cancer KB cells, 1950 MHz RFR induced time-dependent apoptosis (45% after 3 h) that is paralleled by 2.5-fold decrease of the expression of ras and Raf-1 and of the activity of ras and Erk-1/2 (Caraglia et al., 2005). Primary cultured neurons and astrocytes exposed to GSM 1900 MHz RFR for 2 h demonstrated up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) (Zhao et al., 2007). Up-regulation in neurons occurred in both “on” and “stand-by” modes, but in astrocytes only in the “on” mode. We should underline that, in that study an extremely high biological sensitivity to RFR was demonstrated, as a cell phone in the “stand-by” position emits negligibly low-intensity of radiation (up to hundredths  $\mu\text{W}/\text{cm}^2$ ).

Based on the analysis of available literature data, we identified altogether 100 experimental studies in biological models which investigated oxidative stress due to low-intensity RFR exposures. From these 100 articles, 93 studies (93%) demonstrated significant oxidative effects induced by



low-intensity RFR exposure (Table 1–3), while 7 studies (7%) demonstrated the absence of significant changes (Table 4). The total number includes 18 *in vitro* studies, 73 studies in animals, 3 studies in plants and 6 studies in humans. Majority of the research was done on laboratory rats (58 studies, with 54 positive results), while 4 studies out of 6 in humans were positive. From the *in vitro* studies, 17 were positive (94.4%), including 2 studies on human spermatozoa and 2 studies on human blood cells.

Most of the studies utilized RFR exposure in MW range, including a use of commercial or trial cell phones as sources of radiation. The power densities of RFR applied in positive studies varied from  $0.1 \mu\text{W}/\text{cm}^2$  (Oksay et al., 2014) to  $680 \mu\text{W}/\text{cm}^2$  (Jelodar et al., 2013) and SAR values varied from  $3 \mu\text{W}/\text{kg}$  (Burlaka et al., 2013) to the ICNIRP recommended limit of  $2 \text{ W}/\text{kg}$  (Naziroglu et al., 2012a; Xu et al., 2010). Exposure times in positive studies varied from 5 min (Friedman et al., 2007) to 12.5 years, 29.6 h/month (Hamzany et al., 2013).

The most often used indexes of oxidative stress analyzed in the studies were ROS production, levels of lipid peroxidation (LPO)/malondialdehyde (MDA), protein oxidation (PO), nitric oxides ( $\text{NO}_x$ ), glutathione (GSH), activity of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px)). It is important that some studies directly pointed to induction of free radicals (superoxide radical, NO) as a primary reaction of living cells to RFR exposure (Burlaka et al., 2013; Friedman et al., 2007). As we pointed out earlier, direct activation of NADH oxidase (Friedman et al., 2007) and the mitochondrial pathway of superoxide overproduction (Burlaka et al., 2013; De Iuliis et al., 2009) have been experimentally proven. Besides, a significant overproduction of nitrogen oxide was revealed in some studies (Avci et al., 2012; Bilgici et al., 2013; Burlaka et al., 2013), although it is unclear whether an induction of expression of NO-synthases or direct activation of the enzyme took place. It is however clear that significantly increased levels of these free radical species (superoxide and nitrogen oxide) in cells due to RFR exposure result in an activation of peroxidation and repression of activities of key antioxidant enzymes. It is indicative that many studies demonstrated effectiveness of different antioxidants to override oxidative stress caused by RFR exposure. Such effects have been reported for melatonin (Ayata et al., 2004; Lai and Singh, 1997; Oktem et al., 2005; Ozguner et al., 2006; Sokolovic et al., 2008), vitamin E and C (Jelodar et al., 2013; Oral et al., 2006), caffeic acid phenethyl ester (Ozguner et al., 2006), selenium, L-carnitine (Turker et al., 2011) and garlic (Avci et al., 2012; Bilgici et al., 2013).

It is worthwhile to emphasize a strict non-thermal character of ROS overproduction under RFR exposure described in the cited reports. As low as  $0.1 \mu\text{W}/\text{cm}^2$  intensity of RFR and absorbed energy (specific absorption rate, SAR) of  $0.3 \mu\text{W}/\text{kg}$  were demonstrated to be effective in inducing significant oxidative stress in living cells (Burlaka et al., 2013; Oksay et al., 2014). This observation is particularly important as the modern international safety limits on RFR exposure are based solely on the thermal effects of radiation and only restrict RFR intensity to  $450\text{--}1000 \mu\text{W}/\text{cm}^2$  and SAR to  $2 \text{ W}/\text{kg}$  (ICNIRP, 1998). Moreover, studies where

high (thermal) intensities of RFR have been used could not reveal oxidative effects (Hong et al., 2012; Kang et al., 2013; Luukkonen et al., 2009), which might point to the variety of molecular mechanisms for different radiation intensities.

Taken together, the analysis of the contemporary scientific literature on the biological effects of RFR persuasively proves that the exposure to low-intensity RFR in living cells leads to generation of significant levels of ROS and results in a significant oxidative stress.

### Oxidative damage of DNA under RFR exposure

To date more than hundred papers have been published on mutagenic effects of RFR and most of them revealed significant effects (Ruediger, 2009). There is a substantial number of studies which demonstrated the formation of micronuclei (Garaj-Vrhovac et al., 1992; Tice et al., 2002; Zotti-Martelli et al., 2005) or structural anomalies of metaphase chromosomes (Garson et al., 1991; Kerbacher et al., 1990; Maes et al., 2000) in living cells due to low-intensity RFR exposure. However, majority of the studies on the mutagenic effects of RFR successfully used a comet assay approach (Baohong et al., 2005; Belyaev et al., 2006; Diem et al., 2005; Kim et al., 2008; Lai and Singh, 1996; Liu et al., 2013a). Particular studies identified specific marker of oxidative damage of DNA, 8-hydroxy-2'-deoxyguanosine (8-OH-dG) (Burlaka et al., 2013; De Iuliis et al., 2009; Guler et al., 2012; Khalil et al., 2012; Xu et al., 2010). Thus, the level of 8-OH-dG in human spermatozoa was shown to be significantly increased after *in vitro* exposure to low-intensity RFR (De Iuliis et al., 2009). Likewise, we demonstrated that the exposure of quail embryos *in ovo* to GSM 900 MHz of  $0.25 \mu\text{W}/\text{cm}^2$  during a few days was sufficient for a significant, two-threefold, increase of 8-OH-dG level in embryonic cells (Burlaka et al., 2013).

It would be logical to assume that most mutagenic effects due to the RFR exposure are caused by oxidative damage to DNA, as the overproduction of ROS in living cells due to RFR exposure was reliably documented. It is known that superoxide itself does not affect DNA. The most aggressive form of ROS, which is able to affect the DNA molecule directly, is hydroxyl radical (Halliwell, 2007). The hydroxyl radicals are generated in cell in the Fenton reaction ( $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^\bullet + \text{OH}^-$ ) and in the Haber–Weiss reaction ( $\text{O}_2^{\bullet-} + \text{H}_2\text{O}_2 \rightarrow \text{O}_2 + \text{OH}^\bullet + \text{OH}^-$ ) (Valko et al., 2006). On the other hand, increased concentration of NO in addition to superoxide in the RFR-exposed cells can lead to the formation of other aggressive form of ROS, peroxynitrite ( $\text{ONOO}^-$ ), which can also cause DNA damage (Valko et al., 2006).

### Free radicals induced under the RFR exposure can perturb cellular signaling

Taking into account the abovementioned data, we can state that the exposure to RFR leads to overproduction of free radicals/ROS in living cell. Certainly, free radicals can induce harmful effects via direct damage due to oxidation of biological macromolecules. To that, it becomes clear nowadays that free radicals/ROS are an intrinsic part of the cellular signaling cascades (Forman et al., 2014). Thus, hydrogen peroxide appears as a second messenger both in

Table 1. Publications which reported positive findings on oxidative stress caused by RFR exposure of cells *in vitro*.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Agarwal et al., 2009)	Human spermatozoa	Cell phone RFR, in talk mode, for 1 h	Increase in reactive oxygen species (ROS) level, decrease in sperm motility and viability.
(Campisi et al., 2010)	Rat astroglial cells	900 MHz (continuous or modulated), electric field 10 V/m, for 5; 10; 20 min	Increase in ROS levels and DNA fragmentation after exposure to modulated RFR for 20 min.
(De Iuliis et al., 2009)	Human spermatozoa	1.8 GHz, SAR = 0.4–27.5 W/kg	Increased amounts of ROS.
(Friedman et al., 2007)	HeLa membranes	875 MHz, 200 $\mu$ W/cm <sup>2</sup> , for 5 and 10 min	Increased NADH oxidase activity.
(Hou et al., 2014)	Mouse embryonic fibroblasts (NIH/3T3)	1800-MHz GSM-talk mode RFR, SAR = 2 W/kg, intermittent exposure (5 min on/10 min off) for 0.5–8 h	Increased intracellular ROS levels.
(Kahya et al., 2014)	Cancer cell cultures	900 MHz RFR, SAR = 0.36 W/kg, for 1 h	Induced apoptosis effects through oxidative stress, selenium counteracted the effects of RFR exposure.
(Lantow et al., 2006a)	Human blood cells	Continuous wave or GSM signal, SAR = 2 W/kg, for 30 or 45 min of continuous or 5 min ON, 5 min OFF	After continuous or intermittent GSM signal a different ROS production was detected in human monocytes compared to sham.
(Lantow et al., 2006b)	Human Mono Mac 6 and K562 cells	Continuous wave, GSM speaking only, GSM hearing only, GSM talk, SARs of 0.5, 1.0, 1.5 and 2.0 W/kg.	The GSM-DTX signal at 2 W/kg produced difference in free radical production compared to sham.
(Liu et al., 2013b)	GC-2 cells	1800 MHz, SAR = 1; 2 W/kg, 5 min ON, 10 min OFF for 24 h	In the 2 W/kg exposed cultures, the level of ROS was increased.
(Lu et al., 2012)	Human blood mononuclear cells	900 MHz, SAR = 0.4 W/kg, for 1–8 h	The increased level of apoptosis induced through the mitochondrial pathway and mediated by activating ROS and caspase-3.
(Marjanovic et al., 2014)	V79 cells	1800 MHz, SAR = 1.6 W/kg, for 10, 30 and 60 min	ROS level increased after 10 min of exposure. Decrease in ROS level after 30-min treatment indicating antioxidant defense mechanism activation.
(Naziroglu et al., 2012b)	HL-60 cells	2450 MHz, pulsed, SAR = 0.1–2.5 W/kg, for 1; 2; 12 or 24 h	Lipid peroxide (LPO) levels were increased at all exposure times.
(Ni et al., 2013)	Human lens epithelial cells	1800 MHz, SAR = 2; 3; 4 W/kg	The ROS and malondialdehyde (MDA) levels were increased.
(Pilla, 2012)	Neuronal cells and human fibroblasts	27.12 MHz, pulsed, electric field 41 V/m, 2 min prior to lipopolysaccharide administration or for 15 min	Increased level of nitric oxide (NO).
(Sefidbakht et al., 2014)	HEK293T cells	940 MHz, SAR = 0.09 W/kg, for 15, 30, 45, 60 and 90 min	ROS generation increased in the 30 min exposed cells. A sharp rise in catalase (CAT) and superoxide dismutase (SOD) activity and elevation of glutathione (GSH) during the 45 min exposure.
(Xu et al., 2010)	Primary cultured neurons	1800 MHz, pulsed, SAR = 2 W/kg, for 24 h	An increase in the levels of 8-hydroxy-2'-deoxyguanosine (8-OH-dG).
(Zmyslony et al., 2004)	Rat lymphocytes	930 MHz, PD of 500 $\mu$ W/cm <sup>2</sup> , SAR = 1.5 W/kg, for 5 and 15 min	Intracellular ROS level increased in exposed FeCl <sub>2</sub> treated cells compared with unexposed FeCl <sub>2</sub> treated cells.

\*All effects were statistically significant (at least  $p < 0.05$ ) as compared to control or sham exposed groups.

insulin signaling and in growth factor-induced signalling cascades (Sies, 2014). These species are also implicated in biochemical mechanism of oxidation of ethanol and in other metabolic processes (Oshino et al., 1975) and is also required for initiation of wound repair (Enyedi and Niethammer, 2013). In addition, ROS at relatively low concentrations can modulate inflammation via activation of NF- $\kappa$ B pathway (Hayden and Ghosh, 2011). Therefore, even subtle exposures

to RFR with generation of hardly detectable quantities of free radicals can have their meaningful biological consequences.

We could ascertain the signaling effects of moderate levels of free radicals from our experiments in quail embryos irradiated with the commercial cell phone. Thus, we were able to show that the prolonged exposures of embryos *in ovo* led to robust repression of their development (Tsybulin et al., 2013), which was concomitant with



Table 2. Publications which reported positive findings on oxidative stress caused by RFR exposure of animals and plants.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Akbari et al., 2014)	Rat whole body	RFR from base transceiver station	Glutathione peroxidase (GSH-Px), SOD, and CAT activity decreased and level of MDA increased. Vitamin C reduced the effect.
(Al-Damegh, 2012)	Rat whole body	Cell phone RFR, 15, 30, or 60 min/day for 2 weeks	Levels of conjugated dienes, LPO and CAT activities in serum and testicular tissue increased, the total serum and testicular tissue GSH and GSH-Px levels decreased.
(Avci et al., 2012)	Rat whole body	1800 MHz, SAR = 0.4 W/kg, 1 h/day for 3 weeks	An increased level of protein oxidation (PO) in brain tissue and an increase in serum NO. Garlic administration reduced protein oxidation in brain tissue.
(Ayata et al., 2004)	Rat whole body	900 MHz, 30 min/day for 10 days	MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased, and superoxide dismutase (SOD) activity was decreased in skin. Melatonin treatment reversed effect.
(Aynali et al., 2013)	Rat whole body	2450 MHz, pulsed, SAR = 0.143 W/kg, 60 min/day for 30 days	LPO was increased, an administration of melatonin prevented this effect.
(Balci et al., 2007)	Rat whole body	“Standardized daily dose” of cell phone RFR for 4 weeks	In corneal tissue, MDA level and CAT activity increased, whereas SOD activity was decreased. In the lens tissues, the MDA level was increased.
(Bilgici et al., 2013)	Rat whole body	850–950 MHz, SAR = 1.08 W/kg, 1 h/day for 3 weeks	The serum NO levels and levels of MDA and the PO in brain were increased. An administration of garlic extract diminished these effects.
(Bodera et al., 2013)	Rat whole body	1800 MHz, GSM, for 15 min	Reduced antioxidant capacity both in healthy animals and in those with paw inflammation.
(Burlaka et al., 2013)	Quail embryo <i>in ovo</i>	GSM 900 MHz, power density (PD) of 0.25 $\mu\text{W}/\text{cm}^2$ , SAR = 3 $\mu\text{W}/\text{kg}$ , 48 sec ON - 12 sec OFF, for 158–360 h	Overproduction of superoxide and NO, increased levels of thiobarbituric acid reactive substances (TBARS) and 8-OH-dG, decreased SOD and CAT activities.
(Burlaka et al., 2014)	Male rat whole body	Pulsed and continuous MW in the doses equivalent to the maximal permitted energy load for the staffs of the radar stations	Increased rates of superoxide production, formation of the iron-nitrosyl complexes and decreased activity of NADH-ubiquinone oxidoreductase complex in liver, cardiac and aorta tissues 28 days after the exposure.
(Cenesiz et al., 2011)	Guinea pig whole body	900; 1800 MHz RFR from base station antennas, 4 h/day for 20 days	Difference in guinea pigs subjected to 900 and 1800 MHz for plasma oxidant status levels. NO level changed in 900 MHz subjected guinea pigs, as compared to the control.
(Cetin et al., 2014)	Pregnant rats and offspring	900; 1800 MHz RFR, 1 h/day during pregnancy and neonatal development	Brain and liver GSH-Px activities, selenium concentrations in the brain and liver vitamin A and $\beta$ -carotene concentrations decreased in offspring.
(Dasdag et al., 2009)	Head of rats	900 MHz, 2 h/day for 10 months	The total antioxidant capacity and CAT activity in brains were higher than that in the sham group.

(continued)

Table 2. Continued

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Dasdag et al., 2012)	Head of rats	900 MHz, cell-phones-like, 2 h/day for 10 months	Protein carbonyl level was higher in the brain of exposed rats.
(Dasdag et al., 2008)	Rat whole body	900 MHz, PD of 78 $\mu\text{W}/\text{cm}^2$ , 2 h/days for 10 months.	Increased levels of MDA and total oxidative status in liver tissue.
(Deshmukh et al., 2013)	Rat whole body	900 MHz, 2 h/day, 5 days a week for 30 days	The levels of LPO and PO were increased.
(Esmekaya et al., 2011)	Rat whole body	900 MHz, pulsed, modulated, SAR = 1.2 W/kg, 20 min/day for 3 weeks	The increased level of MDA and NOx, and decreased levels of GSH in liver, lung, testis and heart tissues.
(Furtado-Filho et al., 2014)	Rat whole body	950 MHz, SAR = 0.01–0.88 W/kg, 30 min/day for 21 days during pregnancy (or additionally 6 or 15 days of postnatal period)	Neonatal rats exposed in utero had decreased levels of CAT and lower LPO, and genotoxic effect.
(Guler et al., 2012)	Rabbit infant whole body	GSM 1800 MHz, 15 min/day for 7 days (females) or 14 days (males)	LPO levels in the liver tissues of females and males increased, liver 8-OH-dG levels of females were increased.
(Guney et al., 2007)	Rat whole body	900 MHz, 30 min/day for 30 days	Endometrial levels of NO and MDA increased, endometrial SOD, CAT and GSH-Px activities were decreased. Vitamin E and C treatment prevented these effects.
(Gürler et al., 2014)	Rat whole body	2450 MHz, 3.68 V/m, 1 h/day for 30 days	Increased 8-OH-dG level in both plasma and brain tissue whereas it increased PO level only in plasma. Garlic prevented the increase of 8-OH-dG level in brain tissue and plasma PO levels.
(Ilhan et al., 2004)	Rat whole body	900 MHz, from cell phone, 1 h/day for 7 days	Increase in MDA, NO levels, and xanthine oxidase (XO) activity, decrease in SOD and GSH-Px activities in brain. These effects were prevented by Ginkgo biloba extract treatment.
(Jelodar, et al., 2013)	Rat whole body	900 MHz, PD of 680 $\mu\text{W}/\text{cm}^2$ , 4 h/day for 45 days,	The concentration of MDA was increased and activities of SOD, GSH-Px and CAT were decreased in rat eyes. An administration of vitamin C prevented these effects.
(Jelodar et al., 2013)	Rat whole body	900 MHz, daily for 45 days	Increased level of MDA and decreased antioxidant enzymes activity in rat testis.
(Jing et al., 2012)	Rat whole body	Cell phone RFR, SAR = 0.9 W/kg, 3 x 10; 30 or 60 min for 20 days during gestation	After 30 and 60 min the level of MDA was increased, the activities of SOD and GSH-Px were decreased.
(Kerman & Senol, 2012)	Rat whole body	900 MHz, 30 min/day for 10 days	Tissue MDA levels were increased, SOD, CAT and GSH-Px activities were reduced. Melatonin treatment reversed these effects.
(Kesari et al., 2010)	Male rat whole body	Cell phone RFR, SAR = 0.9 W/kg, 2 h/day for 35 days	Reduction in protein kinase activity, decrease in sperm count and increase in apoptosis.
(Kesari et al., 2011)	Rat whole body	900 MHz, pulsed, SAR = 0.9 W/kg, 2 h/day for 45 days	Increase in the level of ROS, decrease in the activities of SOD and GSH-Px, and in the level of pineal melatonin.
(Kesari et al., 2013)	Rat whole body	2115 MHz, SAR = 0.26 W/kg, 2 h/day for 60 days	The level of ROS, DNA damage and the apoptosis rate were increased.
(Khalil et al., 2012)	Rat whole body	1800 MHz, electric field 15–20 V/m, for 2 h	Elevations in the levels of 8-OH-dG in urine.

(continued)

Table 2. Continued

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Kismali et al., 2012)	Rabbit whole body (non-pregnant and pregnant)	1800 MHz, GSM modulation, 15 min/day for 7 days	Creatine kinases levels' changes.
(Koc et al., 2013)	Male rat whole body	Cell phone RFR at calling or stand-by	Oxidative stress detected at both calling and stand-by exposures.
(Koylu et al., 2006)	Rat whole body	900 MHz	The levels of LPO in the brain cortex and hippocampus increased. These levels in the hippocampus were decreased by melatonin administration.
(Koyu et al., 2009)	Rat whole body	900 MHz	The activities of XO, CAT and level of LPO increased in liver. XO, CAT activities and LPO levels were decreased by caffeic acid phenethyl ester (CAPE) administration.
(Kumar et al., 2014)	Rat whole body	Cell phone 1910.5 MHz RFR, 2 h/day for 60 days (6 days a week).	Increase in LPO, damage in sperm cells and DNA damage.
(Lai & Singh, 1997)	Rat whole body	2450 MHz, pulsed, PD = 2 mW/cm <sup>2</sup> , SAR = 1.2 W/kg	Melatonin or spin-trap compound blocked DNA strand breaks induced by RFR exposure in rat brain cells.
(Luo et al., 2014)	Rat whole body	900 MHz imitated cell phone RFR, 4 h/day for 12 days	Contents of liver MDA and Nrf2 protein increased, contents of liver SOD and GSH decreased.
(Mailankot et al., 2009)	Rat whole body	900/1800 MHz, GSM, 1 h/day for 28 days	Increase in LPO and decreased GSH content in the testis and epididymis.
(Manta et al., 2013)	Drosophila whole body	1880–1900 MHz, DECT modulation, SAR = 0.009 W/kg, for 0.5–96 h	Increase in ROS levels in male and female bodies, a quick response in ROS increase in ovaries.
(Marzook et al., 2014)	Rat whole body	900 MHz from cellular tower, 24 h/day for 8 weeks	SOD and CAT activities were reduced in blood, sesame oil reversed the effect
(Meena et al., 2013)	Rat whole body	2450 MHz, PD of 210 $\mu$ W/cm <sup>2</sup> , SAR = 0.14 W/kg, 2 h/day for 45 days	Increased level of MDA and ROS in testis. Melatonin prevented oxidative stress.
(Megha et al., 2012)	Rat whole body	900; 1800 MHz, PD of 170 $\mu$ W/cm <sup>2</sup> , SAR = 0.6 mW/kg, 2 h/day, 5 days/week for 30 days	The levels of the LPO and PO were increased; the level of GSH was decreased.
(Meral et al., 2007)	Guinea pig whole body	890–915 MHz, from cell phone, SAR = 0.95 W/kg, 12 h/day for 30 days (11 h stand-by and 15 min spiking mode)	MDA level increased, GSH level and CAT activity were decreased in the brain. MDA, vitamins A, D <sub>3</sub> and E levels and CAT enzyme activity increased, and GSH level was decreased in the blood.
(Motawi et al., 2014)	Rat whole body	Test cellphone RFR, SAR = 1.13 W/kg, 2 h/day for 60 days	Increments in conjugated dienes, protein carbonyls, total oxidant status and oxidative stress index along with a reduction of total antioxidant capacity levels.
(Naziroglu & Gumral, 2009)	Rat whole body	2450 MHz, 60 min/day for 28 days	Decrease of the cortex brain vitamin A, vitamin C and vitamin E levels.
(Naziroglu et al., 2012a)	Rat whole body	2450 MHz, 60 min/day for 30 days	LPO, cell viability and cytosolic Ca <sup>2+</sup> values in dorsal root ganglion neurons were increased.
(Oksay et al., 2014)	Rat whole body	2450 MHz, pulsed, PD of 0.1 $\mu$ W/cm <sup>2</sup> , SAR = 0.1 W/kg, 1 h/day for 30 days	LPO was higher in exposed animals. Melatonin treatment reversed the effect.
(Oktem et al., 2005)	Rat whole body	900 MHz, 30 min/day for 10 days	Renal tissue MDA level increased, SOD, CAT and GSH-Px activities were reduced. Melatonin treatment reversed these effects.
(Oral et al., 2006)	Rat whole body	900 MHz, 30 min/day for 30 days	Increased MDA levels and apoptosis in endometrial tissue. Treatment with vitamins E and C diminished these changes.

(continued)

Table 2. Continued

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Ozguner et al., 2005a)	Rat whole body	900 MHz, 30 min/day for 10 days	Heart tissue MDA and NO levels increased, SOD, CAT and GSH-Px activities were reduced. CAPE treatment reversed these effects.
(Ozguner et al., 2006)	Rat whole body	900 MHz, from cell phone	Retinal levels of NO and MDA increased, SOD, GSH-Px and CAT activities were decreased. Melatonin and CAPE treatment prevented effects.
(Ozguner et al., 2005b)	Rat whole body	900 MHz	Renal tissue MDA and NO levels increased, the activities of SOD, CAT and GSH-Px were reduced. CAPE treatment reversed these effects.
(Ozgur et al., 2010)	Guinea pig whole body	1800 MHz, GSM, SAR = 0.38 W/kg, 10 or 20 min/day for 7 days	Increases in MDA and total NO(x) levels and decreases in activities of SOD, myeloperoxidase and GSH-Px in liver. Extent of oxidative damage was proportional to the duration of exposure.
(Ozgur et al., 2013)	Rabbit whole body	1800 MHz, pulsed, 15 min/day for 7 days in pregnant animals, for 7 or 15 days in infants	The amount of LPO was increased in the prenatal exposure group.
(Özorak et al., 2013)	Rat whole body	900; 1800; 2450 MHz, pulsed, PD of 12 $\mu\text{W}/\text{cm}^2$ . SAR = 0.18; 1.2 W/kg, 60 min/day during gestation and 6 weeks following delivery	At the age of six weeks, an increased LPO in the kidney and testis, and decreased level of GSH and total antioxidant status.
(Qin et al., 2014)	Male mouse whole body	1800 MHz, 208 $\mu\text{W}/\text{cm}^2$ , 30 or 120 min/d for 30 days	Decreased activities of CAT and GSH-Px and increased level of MDA in cerebrum. Nano-selenium decreased MDA level, and increased GSH-Px and CAT activities.
(Ragy, 2014)	Rat whole body	Cell phone 900 MHz RFR, 1 h/d for 60 days	Increase in MDA levels and decrease total antioxidant capacity levels in brain, liver and kidneys tissues. These alterations were corrected by withdrawal of RFR exposure during 30 days.
(Saikhedkar et al., 2014)	Rat whole body	Cell phone 900 MHz RFR, 4 h/d for 15 days	A significant change in level of antioxidant enzymes and non-enzymatic antioxidants, and an increase in LPO.
(Shahin et al., 2013)	Mouse whole body	2450 MHz, PD of 33.5 $\mu\text{W}/\text{cm}^2$ , SAR = 23 mW/kg, 2 h/day for 45 days	An increase in ROS, decrease in NO and antioxidant enzymes activities.
(Sharma et al., 2009)	Plant(mung bean) whole body	900 MHz, from cell phone, PD of 8.55 $\mu\text{W}/\text{cm}^2$ ; for 0.5; 1; 2, and 4 h	Increased level of MDA, $\text{H}_2\text{O}_2$ accumulation and root oxidizability, upregulation in the activities of SOD, CAT, ascorbate peroxidases, guaiacol peroxidases and GSH reductases in roots.
(Singh et al., 2012)	Plant (mung bean) whole body	900 MHz, from cell phone	The increased level of MDA, hydrogen peroxide and proline content in hypocotyls.
(Sokolovic et al., 2008)	Rat whole body	RFR from cell phone, SAR = 0.043–0.135 W/kg, for 20, 40 and 60 days	An increase in the brain tissue MDA and carbonyl group concentration. Decreased activity of CAT and increased activity of xanthine oxidase (XO). Melatonin treatment prevented the effects.

(continued)

Table 2. Continued

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Sokolovic et al., 2013)	Rat whole body	900 MHz, SAR = 0.043–0.135 W/kg, 4 h/day for 29; 40 or 60 days,	The level of LPO and PO, activities of CAT, XO, number of apoptotic cells were increased in thymus tissue. An administration of melatonin prevented these effects.
(Suleyman et al., 2004)	Rat whole body	Cell phone RFR, SAR = 0.52 W/kg, 20 min/day for 1 month	MDA concentration was increased in brains.
(Tkalec et al., 2007)	Plant <i>Lemna minor</i> (duckweed)	400 and 900 MHz, 10, 23, 41 and 120 V/m, for 2 or 4 h	LPO and H <sub>2</sub> O <sub>2</sub> content increased: CAT activity increased, pyrogallol peroxidase decreased.
(Tkalec et al., 2013)	Earthworm whole body	900 MHz, PD of 30–3800 $\mu$ W/cm <sup>2</sup> , SAR = 0.13–9.33 mW/kg, for 2 h	The protein carbonyl content was increased in all exposures above 30 $\mu$ W/cm <sup>2</sup> . The level of MDA was increased at 140 $\mu$ W/cm <sup>2</sup> .
(Tök et al., 2014)	Rat whole body	2450 MHz, Wi-Fi RFR, 60 min/day for 30 days	Decreased GSH-Px activity. GSH-Px activity and GSH values increased after melatonin treatment.
(Tomruk et al., 2010)	Rabbit whole body	1800 MHz, GSM-like signal, 15 min/day for a week	Increase of MDA and ferrous oxidation in xylenol orange levels.
(Tsybulin et al., 2012)	Quail embryo <i>in ovo</i>	900 MHz, from cell phone, GSM, PD of 0.024–0.21 $\mu$ W/cm <sup>2</sup> , intermittent for 14 days	Increased level of TBARS in brains and livers of hatchlings.
(Turker et al., 2011)	Rat partial body	2450 MHz, pulsed, SAR = 0.1 W/kg, 1 h/day for 28 days	The increased level of LPO, the decreased concentrations of vitamin A, vitamin C and vitamin E. There was a protective effect of selenium and L-carnitine.
(Türedi et al., 2014)	Pregnant rat whole body	900 MHz, 13.7 V/m, 50 $\mu$ W/cm <sup>2</sup> , 1 h/day for 13–21 days of pregnancy	MDA, SOD and CAT values increased, GSH values decreased in exposed pups.
(Yurekli et al., 2006)	Rat whole body	945 MHz, GSM, PD of 367 $\mu$ W/cm <sup>2</sup> , SAR = 11.3 mW/kg	MDA level and SOD activity increased, GSH concentration was decreased.

\*All effects were statistically significant (at least  $p < 0.05$ ) as compared to control or sham exposed groups.

Table 3. Publications which reported positive findings on oxidative stress caused by RFR exposure of humans.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Abu Khadra et al., 2014)	Human male head	GSM 1800 MHz from cell phone, SAR = 1.09 W/kg, for 15 and 30 min	SOD activity in saliva increased.
(Garaj-Vrhovac et al., 2011)	Human whole body	3; 5.5; 9.4 GHz, pulsed, from radars	Increased level of MDA, decreased level of GSH.
(Hamzany et al., 2013)	Human head/whole body	RFR from cell phone a mean time of 29.6 h/month for 12.5 years	Increase in all salivary oxidative stress indices.
(Moustafa et al., 2001)	Human male body	Cell phone in a pocket in standby position, for 1; 2 or 4 h	Plasma level of LPO was increased, activities of SOD and GSH-Px in erythrocytes decreased.

\*All effects were statistically significant (at least  $p < 0.05$ ) as compared to control or sham-exposed groups.

significant overproduction of superoxide radical and NO radical, increased rates of lipid peroxidation and oxidative damage of DNA (Burlaka et al., 2013; Tsybulin et al., 2012). Notably, shorter exposures instead led to enhancement in embryonic development (Tsybulin et al., 2012, 2013). We demonstrated the favorable effects of shorter exposures also on the molecular level. Thus, after the short-time RFR exposure the DNA comets in embryonic cells were significantly shorter than in the control non-irradiated embryos, pointing to activation of mechanisms maintaining

the integrity of DNA. The “beneficial” consequences of the irradiation could be explained by hormesis effect (Calabrese, 2008). However, one could hypothesize that the “beneficial” effects of the irradiation could be explained by the signaling action of free radicals induced at levels below the damaging concentrations. Obviously, any seemingly beneficial effect of external environmental impact should be treated with caution and possibly minimized before careful evaluation of the long-term consequences. Altogether, this gives a clear warning of the adverse health effects of



Table 4. Publications which reported no significant oxidative effects after RFR exposure.

Reference	Biological system exposed	RFR exposure	Effects reported
(Hook et al., 2004)	Mammalian cells <i>in vitro</i>	835.62 MHz (frequency-modulated continuous-wave, FMCW) and 847.74 MHz (code division multiple access, CDMA), SAR = 0.8 W/kg, for 20–22 h	FMCW- and CDMA-modulated RFR did not alter parameters indicative of oxidative stress.
(Ferreira et al., 2006a)	Rat whole body	800–1800 MHz, from cell phone	No changes in lipid and protein damage, and in non-enzymatic anti-oxidant defense in frontal cortex or hippocampus.
(Ferreira et al., 2006b)	Pregnant rat whole body	RFR from cell phone	No differences in oxidative parameter of offspring blood and liver, but increase in erythrocytes micronuclei incidence in offspring.
(Dasdag et al., 2003)	Rat whole body	Cell phone RFR, SAR = 0.52 W/kg, 20 min/day for 1 month	No alteration in MDA concentration.
(Demirel et al., 2012)	Rat whole body	3G cell phone RFR, “standardized daily dose” for 20 days	No difference in GSH-Px and CAT activity in eye tissues, in MDA and GSH levels in blood.
(Khalil et al., 2014)	Human head/whole body	Cell phone RFR (talking mode) for 15 or 30 min	No relationship between exposure and changes in the salivary oxidant/anti-oxidant profile.
(de Souza et al., 2014)	Human head/whole body	Cell phone RFR	No difference in the saliva from the parotid gland exposed to cell phone RFR to the saliva from the opposite gland of each individual.

low-intensity RFR, which could be evoked both by the direct oxidative damage and by disturbed cellular signaling.

### Oxidative effects and non-cancer health effects of RFR

A new medical condition, so-called electrohypersensitivity (EHS), in which people suffer due to RFR exposure, has been described (Johansson, 2006). Typically, these persons suffer from skin- and mucosa-related symptoms (itching, smarting, pain, heat sensation), or heart and nervous system disorders after exposure to computer monitors, cell phones and other electromagnetic devices. This disorder is growing continuously: starting from 0.06% of the total population in 1985, this category now includes as much as 9–11% of the European population (Hallberg and Oberfeld, 2006). In Sweden, for example, EHS has become an officially recognized health impairment.

To that, a high percentage, up to 18–43% of young people, has recently been described to be suffering from headache/earache during or after cell phone conversations (Chu et al., 2011; Yakymenko et al., 2011). Likewise, a number of psychophysical and preclinical disorders including fatigue, irritation, headache, sleep disorders, hormonal imbalances were detected in high percent of people living nearby cell phone base transceiver stations (Buchner and Eger, 2011; Santini et al., 2002).

An allergy reaction to RFR in humans has been confirmed by a significant increase in the level of mast cells in skin of persons under exposure to electromagnetic devices (Johansson et al., 2001). Likewise, higher level of degranulated mast cells in dermis of EHS persons has been detected (Johansson, 2006). In turn, the activated mast cells can release histamine and other mediators of such reactions which include allergic hypersensitivity, itching, dermatoses, etc.

Importantly, an implication of ROS in allergic reactions is rather clear nowadays. For example, in case of airway allergic inflammation, the lung cells generate superoxide in nanomolar concentrations following antigen challenges (Nagata, 2005). Then, mast cells generate ROS following aggregation of FcεRI, a high-affinity IgE receptor (Okayama, 2005). In addition, pollen NADPH oxidases rapidly increase the level of ROS in lung epithelium (Boldogh et al., 2005); and removal of pollen NADPH oxidases from the challenge material reduced antigen-induced allergic airway inflammation. Thus, it seems plausible that EHS-like conditions can be attributed at least partially to ROS overproduction in cells due to RFR exposures.

### Oxidative effects and potential carcinogenicity of RFR

During recent years, a number of epidemiological studies indicated a significant increase in incidence of various types of tumors among long-term or “heavy” users of cellular phones (Yakymenko et al., 2011). Briefly, reports pointed to the increased risk in brain tumors (Cardis et al., 2010; Hardell and Carlberg, 2009; Hardell et al., 2007), acoustic neuroma (Hardell et al., 2005; Sato et al., 2011), tumors of parotid glands (Sadetzki et al., 2008), seminomas (Hardell et al., 2007), melanomas (Hardell et al., 2011) and lymphomas (Hardell et al., 2005) in these cohorts of people. To that, a significant increase in tumor incidence among people living nearby cellular base transceiver stations was also reported (Eger et al., 2004; Wolf and Wolf, 2007). Similarly, experimental evidences of cancer expansion in rodents caused by long-term low-intensity RFR exposure were published (Chou et al., 1992; Repacholi et al., 1997; Szmigielski et al., 1982; Toler et al., 1997). To that, activation of ODC was detected in RFR-exposed cells (Hoyto et al., 2007). ODC is involved in

processes of cell growth and differentiation, and its activity is increased in tumor cells. Although overexpression of ODC is not sufficient for tumorigenic transformation, an increased activity of this enzyme was shown to promote the development of tumors from pre-tumor cells (Clifford et al., 1995).

Significant overproduction of ROS leads to oxidative stress in living cells, induces oxidative damage of DNA and can cause malignant transformation (Halliwell and Whiteman, 2004; Valko et al., 2007). It is known that in addition to mutagenic effects, ROS play a role as a second messenger for intracellular signaling cascades which can also induce oncogenic transformation (Valko et al., 2006). Earlier we hypothesized (Burlaka et al., 2013) that low-intensity RFR exposure leads to dysfunctions of mitochondria, which result in overproduction of superoxide and NO, and subsequently to ROS-mediated mutagenesis. To that, it is well established that oxidative stress is associated with carcinogenesis; for instance, the oxidative stress elicited by Membrane-Type 1 Matrix Metalloproteinase is implicated in both the pathogenesis and progression of prostate cancer (Nguyen et al., 2011). Similarly, a progressive elevation in mitochondrial ROS production (chronic ROS) under both hypoxia and/or low glucose, which leads to stabilization of cells via increased HIF-2 $\alpha$  expression, can eventually result in malignant transformation (Ralph et al., 2010). These data, together with the strong experimental evidences on activation of NADH oxidase under RFR exposure (Friedman et al., 2007) suggest that low-intensity RFR is a multifactorial stress factor for living cell, significant feature of which is oxidative effects and potential carcinogenicity as a result.

## Conclusions

The analysis of modern data on biological effects of low-intensity RFR leads to a firm conclusion that this physical agent is a powerful oxidative stressor for living cell. The oxidative efficiency of RFR can be mediated via changes in activities of key ROS-generating systems, including mitochondria and non-phagocytic NADH oxidases, via direct effects on water molecules, and via induction of conformation changes in biologically important macromolecules. In turn, a broad biological potential of ROS and other free radicals, including both their mutagenic effects and their signaling regulatory potential, makes RFR a potentially hazardous factor for human health. We suggest minimizing the intensity and time of RFR exposures, and taking a precautionary approach towards wireless technologies in everyday human life.

## Acknowledgments

The authors are grateful to the unknown referees for the valuable comments on the first version of the manuscript.

## Declaration of interest

The authors declare no conflicts of interest. This study was supported by National Academy of Sciences of Ukraine (I.Y., E.S.) and by University of Campinas via PPVE (Programa Professor Visitante do Exterior), Brazil (S.K.).

## References

- Abdel-Rassoul, G., El-Fateh, O. A., Salem, M. A., et al. (2007). Neurobehavioral effects among inhabitants around mobile phone base stations. *Neurotoxicology* 28:434–440.
- Abu Khadra, K. M., Khalil, A. M., Abu Samak, M., et al. (2014). Evaluation of selected biochemical parameters in the saliva of young males using mobile phones. *Electromagn. Biol. Med.* 32:72–76.
- Agarwal, A., Desai, N. R., Makker, K., et al. (2009). Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: An in vitro pilot study. *Fertil. Steril.* 92:1318–1325.
- Akbari, A., Jelodar, G., Nazifi, S. (2014). Vitamin C protects rat cerebellum and encephalon from oxidative stress following exposure to radiofrequency wave generated by BTS antenna mobile. *Toxicol. Mechanisms Methods* 24:347–352.
- Al-Damegh, M. A. (2012). Rat testicular impairment induced by electromagnetic radiation from a conventional cellular telephone and the protective effects of the antioxidants vitamins C and E. *Clinics* 67:785–792.
- Avci, B., Akar, A., Bilgici, B., et al. (2012). Oxidative stress induced by 1.8 GHz radio frequency electromagnetic radiation and effects of garlic extract in rats. *Int. J. Radiat. Biol.* 88:799–805.
- Ayata, A., Mollaoglu, H., Yilmaz, H. R., et al. (2004). Oxidative stress-mediated skin damage in an experimental mobile phone model can be prevented by melatonin. *J. Dermatol.* 31:878–883.
- Aynali, G., Naziroglu, M., Celik, O., et al. (2013). Modulation of wireless (2.45 GHz)-induced oxidative toxicity in laryngotracheal mucosa of rat by melatonin. *Eur. Arch. Oto-Rhino-Laryngol.* 270: 1695–1700.
- Balci, M., Devrim, E., Durak, I. (2007). Effects of mobile phones on oxidant/antioxidant balance in cornea and lens of rats. *Curr. Eye Res.* 32:21–25.
- Baohong, W., Jiliang, H., Lifan, J., et al. (2005). Studying the synergistic damage effects induced by 1.8 GHz radiofrequency field radiation (RFR) with four chemical mutagens on human lymphocyte DNA using comet assay in vitro. *Mutat. Res.* 578:149–157.
- Belyaev, I. (2010). Dependence of non-thermal biological effects of microwaves on physical and biological variables: Implications for reproducibility and safety standards. *Eur. J. Oncol. Library* 5: 187–217.
- Belyaev, I. Y., Koch, C. B., Terenius, O., et al. (2006). Exposure of rat brain to 915 MHz GSM microwaves induces changes in gene expression but not double stranded DNA breaks or effects on chromatin conformation. *Bioelectromagnetics* 27:295–306.
- Bilgici, B., Akar, A., Avci, B., et al. (2013). Effect of 900 MHz radiofrequency radiation on oxidative stress in rat brain and serum. *Electromagn. Biol. Med.* 32:20–29.
- Blank, M., Soo, L. (2001). Electromagnetic acceleration of electron transfer reactions. *J. Cell Biochem.* 81:278–283.
- Blank, M., Soo, L. (2003). Electromagnetic acceleration of the Belousov-Zhabotinski reaction. *Bioelectrochemistry* 61:93–97.
- Bodera, P., Stankiewicz, W., Zawada, K., et al. (2013). Changes in antioxidant capacity of blood due to mutual action of electromagnetic field (1800 MHz) and opioid drug (tramadol) in animal model of persistent inflammatory state. *Pharmacol. Rep.* 65: 421–428.
- Bohr, H., Bohr, J. (2000a). Microwave-enhanced folding and denaturation of globular proteins. *Phys. Rev. E* 61:4310–4314.
- Bohr, H., Bohr, J. (2000b). Microwave enhanced kinetics observed in ORD studies of a protein. *Bioelectromagnetics* 21:68–72.
- Boldogh, I., Bacsai, A., Choudhury, B. K., et al. (2005). ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation. *J. Clin. Investig.* 115: 2169–2179.
- Buchner, K., Eger, H. (2011). [Changes of clinically important neurotransmitters under the influence of modulated RF fields—A long-term study under real-life conditions]. *Umwelt -Medizin-Gesellschaft* 24: 44–57.
- Budi, A., Legge, F. S., Treutlein, H., et al. (2007). Effect of frequency on insulin response to electric field stress. *J. Phys. Chem. B.* 111: 5748–5756.
- Burlaka, A., Selyuk, M., Gafurov, M., et al. (2014). Changes in mitochondrial functioning with electromagnetic radiation of ultra high

- frequency as revealed by electron paramagnetic resonance methods. *Int. J. Radiat. Biol.* 90:357–362.
- Burlaka, A., Tsybulin, O., Sidorik, E., et al. (2013). Overproduction of free radical species in embryonal cells exposed to low intensity radiofrequency radiation. *Exp. Oncol.* 35:219–225.
- Byus, C. V., Kartun, K., Pieper, S., et al. (1988). Increased ornithine decarboxylase activity in cultured cells exposed to low energy modulated microwave fields and phorbol ester tumor promoters. *Cancer Res.* 48:4222–4226.
- Calabrese, E. J. (2008). Hormesis: Why it is important to toxicology and toxicologists. *Environ. Toxicol. Chem.* 27:1451–1474.
- Campisi, A., Gulino, M., Acquaviva, R., et al. (2010). Reactive oxygen species levels and DNA fragmentation on astrocytes in primary culture after acute exposure to low intensity microwave electromagnetic field. *Neurosci. Lett.* 473:52–55.
- Caraglia, M., Marra, M., Mancinelli, F., et al. (2005). Electromagnetic fields at mobile phone frequency induce apoptosis and inactivation of the multi-chaperone complex in human epidermoid cancer cells. *J. Cell. Physiol.* 204:539–548.
- Cardis, E., Deltour, I., Vrijheid, M., et al. (2010). Brain tumour risk in relation to mobile telephone use: Results of the INTERPHONE international case-control study. *Int. J. Epidemiol.* 39:675–694.
- Cenesis, M., Atakisi, O., Akar, A., et al. (2011). Effects of 900 and 1800 MHz electromagnetic field application on electrocardiogram, nitric oxide, total antioxidant capacity, total oxidant capacity, total protein, albumin and globulin levels in guinea pigs. *Kafkas Üniv. Vet. Fakültesi Dergisi* 17:357–362.
- Céspedes, O., Ueno, S. (2009). Effects of radio frequency magnetic fields on iron release from cage proteins. *Bioelectromagnetics* 30: 336–342.
- Cetin, H., Naziroglu, M., Celik, Ö., et al. (2014). Liver antioxidant stores protect the brain from electromagnetic radiation (900 and 1800 MHz)-induced oxidative stress in rats during pregnancy and the development of offspring. *J. Matern.-Fetal Neonat. Med.* 72:1915–1921.
- Chou, C. K., Guy, A. W., Kunz, L. L., et al. (1992). Long-term, low-level microwave irradiation of rats. *Bioelectromagnetics* 13:469–496.
- Chu, M. K., Song, H. G., Kim, C., et al. (2011). Clinical features of headache associated with mobile phone use: A cross-sectional study in university students. *BMC Neurol.* 11:115.
- Clifford, A., Morgan, D., Yuspa, S. H., et al. (1995). Role of ornithine decarboxylase in epidermal tumorigenesis. *Cancer Res.* 55: 1680–1686.
- Consales, C., Merla, C., Marino, C., et al. (2012). Electromagnetic fields, oxidative stress, and neurodegeneration. *Int. J. Cell Biol.* 2012: 683897.
- Dasdag, S., Akdag, M. Z., Kizil, G., et al. (2012). Effect of 900 MHz radio frequency radiation on beta amyloid protein, protein carbonyl, and malondialdehyde in the brain. *Electromagn. Biol. Med.* 31:67–74.
- Dasdag, S., Akdag, M. Z., Ulukaya, E., et al. (2009). Effect of mobile phone exposure on apoptotic glial cells and status of oxidative stress in rat brain. *Electromagn. Biol. Med.* 28:342–354.
- Dasdag, S., Bilgin, H., Akdag, M. Z., et al. (2008). Effect of long term mobile phone exposure on oxidative-antioxidative processes and nitric oxide in rats. *Biotechnol. Biotechnol. Equip.* 22:992–997.
- Dasdag, S., Zulkuf Akdag, M., Aksen, F., et al. (2003). Whole body exposure of rats to microwaves emitted from a cell phone does not affect the testes. *Bioelectromagnetics* 24:182–188.
- De Iuliis, G. N., Newey, R. J., King, B. V., et al. (2009). Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. *PLoS One* 4: e6446.
- de Souza, F. T., Silva, J. F., Ferreira, E. F., et al. (2014). Cell phone use and parotid salivary gland alterations: No molecular evidence. *Cancer Epidemiol. Biomarkers Prevent.* 23:1428–1431.
- Demirel, S., Doganay, S., Turkoz, Y., et al. (2012). Effects of third generation mobile phone-emitted electromagnetic radiation on oxidative stress parameters in eye tissue and blood of rats. *Cutan. Ocul. Toxicol.* 31:89–94.
- Desai, N. R., Kesari, K. K., Agarwal, A. (2009). Pathophysiology of cell phone radiation: Oxidative stress and carcinogenesis with focus on male reproductive system. *Reprod. Biol. Endocrinol.* 7:114.
- Deshmukh, P. S., Banerjee, B. D., Abegaonkar, M. P., et al. (2013). Effect of low level microwave radiation exposure on cognitive function and oxidative stress in rats. *Indian J. Biochem. Biophys.* 50: 114–119.
- Diem, E., Schwarz, C., Adlkofer, F., et al. (2005). Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro. *Mutat. Res.* 583:178–183.
- Dutta, S. K., Ghosh, B., Blackman, C. F. (1989). Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture. *Bioelectromagnetics* 10: 197–202.
- Eger, H., Hagen, K., Lucas, B., et al. (2004). [Influence of the proximity of mobile phone base stations on the incidence of cancer]. *Environ. Med. Soc.* 17:273–356.
- Enyedi, B., Niethammer, P. (2013). H<sub>2</sub>O<sub>2</sub>: A chemoattractant? *Methods Enzymol.* 528:237–255.
- Esmekaya, M. A., Ozer, C., Seyhan, N. (2011). 900 MHz pulse-modulated radiofrequency radiation induces oxidative stress on heart, lung, testis and liver tissues. *Gen. Physiol. Biophys.* 30:84–89.
- Ferreira, A. R., Bonatto, F., de Bittencourt Pasquali, M. A., et al. (2006a). Oxidative stress effects on the central nervous system of rats after acute exposure to ultra high frequency electromagnetic fields. *Bioelectromagnetics* 27:487–493.
- Ferreira, A. R., Knakievicz, T., Pasquali, M. A., et al. (2006b). Ultra high frequency-electromagnetic field irradiation during pregnancy leads to an increase in erythrocytes micronuclei incidence in rat offspring. *Life Sci.* 80:43–50.
- Forman, H. J., Ursini, F., Maiorino, M. (2014). An overview of mechanisms of redox signaling. *J. Mol. Cell Cardiol.* 73:2–9.
- Friedman, J., Kraus, S., Hauptman, Y., et al. (2007). Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. *Biochem. J.* 405:559–568.
- Furtado-Filho, O. V., Borba, J. B., Dallegrave, A., et al. (2014). Effect of 950 MHz UHF electromagnetic radiation on biomarkers of oxidative damage, metabolism of UFA and antioxidants in the livers of young rats of different ages. *Int. J. Radiat. Biol.* 90:159–168.
- Gandhi, O. P., Morgan, L. L., de Salles, A. A., et al. (2012). Exposure limits: The underestimation of absorbed cell phone radiation, especially in children. *Electromagn. Biol. Med.* 31:34–51.
- Garaj-Vrhovac, V., Fucic, A., Horvat, D. (1992). The correlation between the frequency of micronuclei and specific chromosome aberrations in human lymphocytes exposed to microwave radiation in vitro. *Mutat. Res.* 281:181–186.
- Garaj-Vrhovac, V., Gajski, G., Pažanin, S., et al. (2011). Assessment of cytogenetic damage and oxidative stress in personnel occupationally exposed to the pulsed microwave radiation of marine radar equipment. *Int. J. Hyg. Environ. Health.* 214:59–65.
- Garson, O. M., McRobert, T. L., Campbell, L. J., et al. (1991). A chromosomal study of workers with long-term exposure to radio-frequency radiation. *Med. J. Austral.* 155:289–292.
- Georgiou, C. D. (2010). Oxidative stress-induced biological damage by low-level EMFs: Mechanism of free radical pair electron spin-polarization and biochemical amplification. *Eur. J. Oncol.* 5:63–113.
- Goodman, R., Blank, M. (2002). Insights into electromagnetic interaction mechanisms. *J. Cell Physiol.* 192:16–22.
- Griendling, K. K., Sorescu, D., Ushio-Fukai, M. (2000). NAD(P)H oxidase: Role in cardiovascular biology and disease. *Circ. Res.* 86: 494–501.
- Guler, G., Tomruk, A., Ozgur, E., et al. (2012). The effect of radiofrequency radiation on DNA and lipid damage in female and male infant rabbits. *Int. J. Radiat. Biol.* 88:367–373.
- Guney, M., Ozguner, F., Oral, B., et al. (2007). 900 MHz radiofrequency-induced histopathologic changes and oxidative stress in rat endometrium: Protection by vitamins E and C. *Toxicol. Ind. Health* 23: 411–420.
- Gürler, H. Ş., Bilgici, B., Akar, A. K., et al. (2014). Increased DNA oxidation (8-OHdG) and protein oxidation (AOPP) by low level electromagnetic field (2.45 GHz) in rat brain and protective effect of garlic. *Int. J. Radiat. Biol.* 90:892–896.
- Guzy, R. D., Schumacker, P. T. (2006). Oxygen sensing by mitochondria at complex III: The paradox of increased reactive oxygen species during hypoxia. *Exp. Physiol.* 91:807–819.
- Hallberg, O., Oberfeld, G. (2006). Letter to the editor: Will we all become electrosensitive? *Electromagn. Biol. Med.* 25:189–191.
- Halliwell, B. (1991). Reactive oxygen species in living systems: Source, biochemistry, and role in human disease. *Am. J. Med.* 91: 14S–22S.



- Halliwell, B. (2007). Biochemistry of oxidative stress. *Biochem. Soc. Trans.* 35:1147–1150.
- Halliwell, B., Whiteman, M. (2004). Measuring reactive species and oxidative damage in vivo and in cell culture: How should you do it and what do the results mean? *Br. J. Pharmacol.* 142:231–255.
- Hamzany, Y., Feinmesser, R., Shpitser, T., et al. (2013). Is human saliva an indicator of the adverse health effects of using mobile phones? *Antioxid. Redox. Signal.* 18:622–627.
- Hardell, L., Carlberg, M. (2009). Mobile phones, cordless phones and the risk for brain tumours. *Int. J. Oncol.* 35:5–17.
- Hardell, L., Carlberg, M., Hansson Mild, K. (2005). Case-control study on cellular and cordless telephones and the risk for acoustic neuroma or meningioma in patients diagnosed 2000–2003. *Neuroepidemiology* 25:120–128.
- Hardell, L., Carlberg, M., Hansson Mild, K., et al. (2011). Case-control study on the use of mobile and cordless phones and the risk for malignant melanoma in the head and neck region. *Pathophysiology* 18:325–333.
- Hardell, L., Carlberg, M., Ohlson, C. G., et al. (2007). Use of cellular and cordless telephones and risk of testicular cancer. *Int. J. Androl.* 30: 115–122.
- Hardell, L., Carlberg, M., Soderqvist, F., et al. (2007). Long-term use of cellular phones and brain tumours: Increased risk associated with use for > or = 0 years. *Occup. Environ. Med.* 64:626–632.
- Hardell, L., Eriksson, M., Carlberg, M., et al. (2005). Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma. *Int. Arch. Occup. Environ. Health* 78:625–632.
- Hayden, M. S., Ghosh, S. (2011). NF-kappa B in immunobiology. *Cell Res.* 21:223–244.
- Hong, M. N., Kim, B. C., Ko, Y. G., et al. (2012). Effects of 837 and 1950 MHz radiofrequency radiation exposure alone or combined on oxidative stress in MCF10A cells. *Bioelectromagnetics* 33:604–611.
- Hook, G. J., Spitz, D. R., Sim, J. E., et al. (2004). Evaluation of parameters of oxidative stress after in vitro exposure to FMCW- and CDMA-modulated radiofrequency radiation fields. *Radiat. Res.* 162: 497–504.
- Hou, Q., Wang, M., Wu, S., et al. (2014). Oxidative changes and apoptosis induced by 1800-MHz electromagnetic radiation in NIH/3T3 cells. *Electromagn. Biol. Med.* 34:85–92.
- Hoyto, A., Juutilainen, J., Naarala, J. (2007). Ornithine decarboxylase activity is affected in primary astrocytes but not in secondary cell lines exposed to 872 MHz RF radiation. *Int. J. Radiat. Biol.* 83:367–374.
- Hyland, G. J. (2000). Physics and biology of mobile telephony. *Lancet* 356:1833–1836.
- ICNIRP. (1998). Guidelines for limiting exposure to time-varying electric, magnetic and electromagnetic fields (up to 300 GHz). *Health Phys.* 74:494–522.
- Ilhan, A., Gurel, A., Armutcu, F., et al. (2004). Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain. *Clin. Chim. Acta.* 340:153–162.
- Inoue, M., Sato, E. F., Nishikawa, M., et al. (2003). Mitochondrial generation of reactive oxygen species and its role in aerobic life. *Curr. Med. Chem.* 10:2495–2505.
- Jelodar, G., Akbari, A., Nazifi, S. (2013). The prophylactic effect of vitamin C on oxidative stress indexes in rat eyes following exposure to radiofrequency wave generated by a BTS antenna model. *Int. J. Radiat. Biol.* 89:128–131.
- Jelodar, G., Nazifi, S., Akbari, A. (2013). The prophylactic effect of vitamin C on induced oxidative stress in rat testis following exposure to 900 MHz radio frequency wave generated by a BTS antenna model. *Electromagn. Biol. Med.* 32:409–416.
- Jing, J., Yuhua, Z., Xiao-qian, Y., et al. (2012). The influence of microwave radiation from cellular phone on fetal rat brain. *Electromagn. Biol. Med.* 31:57–66.
- Johansson, O. (2006). Electrohypersensitivity: State-of-the-art of a functional impairment. *Electromagn. Biol. Med.* 25:245–258.
- Johansson, O., Gangi, S., Liang, Y., et al. (2001). Cutaneous mast cells are altered in normal healthy volunteers sitting in front of ordinary TVs/PCs – results from open-field provocation experiments. *J. Cutan. Pathol.* 28:513–519.
- Kahya, M. C., Naziroğlu, M., Çiğ, B. (2014). Selenium reduces mobile phone (900 MHz)-induced oxidative stress, mitochondrial function, and apoptosis in breast cancer cells. *Biol. Trace Elem. Res.* 160: 285–293.
- Kang, K. A., Lee, H. C., Lee, J. J., et al. (2013). Effects of combined radiofrequency radiation exposure on levels of reactive oxygen species in neuronal cells. *J. Radiat. Res. (Published online)*:rrt116.
- Kerbacher, J. J., Meltz, M. L., Erwin, D. N. (1990). Influence of radiofrequency radiation on chromosome aberrations in CHO cells and its interaction with DNA-damaging agents. *Radiat. Res.* 123: 311–319.
- Kerman, M., Senol, N. (2012). Oxidative stress in hippocampus induced by 900 MHz electromagnetic field emitting mobile phone: Protection by melatonin. *Biomed. Res.* 23:147–151.
- Kesari, K. K., Kumar, S., Behari, J. (2010). Mobile phone usage and male infertility in Wistar rats. *Indian J. Exp. Biol.* 48:987–992.
- Kesari, K. K., Kumar, S., Behari, J. (2011). 900-MHz microwave radiation promotes oxidation in rat brain. [Research Support, Non-U.S. Gov't]. *Electromagn. Biol. Med.* 30:219–234.
- Kesari, K. K., Meena, R., Nirala, J., et al. (2013). Effect of 3G cell phone exposure with computer controlled 2-D stepper motor on non-thermal activation of the hsp27/p38MAPK stress pathway in rat brain. *Cell Biochem. Biophys.* 68:347–358.
- Khalil, A. M., Abu Khadra, K. M., Aljaberi, A. M., et al. (2014). Assessment of oxidant/antioxidant status in saliva of cell phone users. *Electromagn. Biol. Med.* 32:92–97.
- Khalil, A. M., Gagaa, M. H., Alshamali, A. M. (2012). 8-Oxo-7, 8-dihydro-2'-deoxyguanosine as a biomarker of DNA damage by mobile phone radiation. *Hum. Exp. Toxicol.* 31:734–740.
- Kim, J. Y., Hong, S. Y., Lee, Y. M., et al. (2008). In vitro assessment of clastogenicity of mobile-phone radiation (835 MHz) using the alkaline comet assay and chromosomal aberration test. [Research Support, Non-U.S. Gov't]. *Environ. Toxicol.* 23:319–327.
- Kismali, G., Ozgur, E., Guler, G., et al. (2012). The influence of 1800 MHz GSM-like signals on blood chemistry and oxidative stress in non-pregnant and pregnant rabbits. *Int. J. Radiat. Biol.* 88: 414–419.
- Koc, A., Unal, D., Cimentepe, E. (2013). The effects of antioxidants on testicular apoptosis and oxidative stress produced by cell phones. *Turk. J. Med. Sci.* 43:131–137.
- Koylu, H., Mollaoglu, H., Ozguner, F., et al. (2006). Melatonin modulates 900 MHz microwave-induced lipid peroxidation changes in rat brain. *Toxicol. Ind. Health* 22:211–216.
- Koyu, A., Ozguner, F., Yilmaz, H., et al. (2009). The protective effect of caffeic acid phenethyl ester (CAPE) on oxidative stress in rat liver exposed to the 900 MHz electromagnetic field. *Toxicol. Ind. Health* 25:429–434.
- Kumar, S., Nirala, J. P., Behari, J., et al. (2014). Effect of electromagnetic irradiation produced by 3G mobile phone on male rat reproductive system in a simulated scenario. *Indian J. Exp. Biol.* 52: 890–897.
- Lai, H., Singh, N. P. (1996). Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. *Int. J. Radiat. Biol.* 69:513–521.
- Lai, H., Singh, N. P. (1997). Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. *Bioelectromagnetics* 18:446–454.
- Lantow, M., Lupke, M., Frahm, J., et al. (2006a). ROS release and Hsp70 expression after exposure to 1.800 MHz radiofrequency electromagnetic fields in primary human monocytes and lymphocytes. *Radiat. Environ. Biophys.* 45:55–62.
- Lantow, M., Schuderer, J., Hartwig, C., et al. (2006b). Free radical release and HSP70 expression in two human immune-relevant cell lines after exposure to 1800 MHz radiofrequency radiation. *Radiat. Res.* 165:88–94.
- Litovitz, T. A., Krause, D., Penafiel, M., et al. (1993). The role of coherence time in the effect of microwaves on ornithine decarboxylase activity. *Bioelectromagnetics* 14:395–403.
- Litovitz, T. A., Penafiel, L. M., Farrel, J. M., et al. (1997). Bioeffects induced by exposure to microwaves are mitigated by superposition of ELF noise. *Bioelectromagnetics* 18:422–430.
- Liu, C., Duan, W., Xu, S., et al. (2013a). Exposure to 1800 MHz radiofrequency electromagnetic radiation induces oxidative DNA base damage in a mouse spermatocyte-derived cell line. *Toxicol. Lett.* 218: 2–9.
- Liu, C., Gao, P., Xu, S.-C., et al. (2013b). Mobile phone radiation induces mode-dependent DNA damage in a mouse spermatocyte-derived cell line: A protective role of melatonin. *Int J Radiat Biol.* 89: 993–1001.

- Liu, Y., Fiskum, G., Schubert, D. (2002). Generation of reactive oxygen species by the mitochondrial electron transport chain. *J. Neurochem.* 80:780–787.
- Low, H., Crane, F. L., Morre, D. J. (2012). Putting together a plasma membrane NADH oxidase: a tale of three laboratories. *Int. J. Biochem. Cell Biol.* 44:1834–1838.
- Lu, Y. S., Huang, B. T., Huang, Y. X. (2012). Reactive oxygen species formation and apoptosis in human peripheral blood mononuclear cell induced by 900 MHz mobile phone radiation. *Oxid. Med. Cell Longev.* 2012:740280.
- Luo, Y.-p., Ma, H.-R., Chen, J.-W., et al. (2014). [Effect of American Ginseng Capsule on the liver oxidative injury and the Nrf2 protein expression in rats exposed by electromagnetic radiation of frequency of cell phone]. *Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chin. J. Integr. Tradit. Western Med.* 34: 575–580.
- Luukkonen, J., Hakulinen, P., Maki-Paakkanen, J., et al. (2009). Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872 MHz radiofrequency radiation. *Mutat. Res.* 662:54–58.
- Maes, A., Collier, M., Verschaeve, L. (2000). Cytogenetic investigations on microwaves emitted by a 455.7 MHz car phone. *Folia Biol.* 46: 175–180.
- Maes, W. (2005). *[Stress Caused by Electromagnetic Fields and Radiation]*. Neubeuern, Germany: IBN.
- Mailankot, M., Kunnath, A. P., Jayalekshmi, H., et al. (2009). Radio frequency electromagnetic radiation (RF-EMR) from GSM (0.9/1.8GHz) mobile phones induces oxidative stress and reduces sperm motility in rats. *Clinics* 64:561–565.
- Manta, A. K., Stravopodis, D. J., Papassideri, I. S., et al. (2013). Reactive oxygen species elevation and recovery in Drosophila bodies and ovaries following short-term and long-term exposure to DECT base EMF. *Electromagn. Biol. Med.* 33:118–131.
- Marino, A. A., Carrubba, S., Frilot, C., et al. (2009). Evidence that transduction of electromagnetic field is mediated by a force receptor. *Neurosci. Lett.* 452:119–123.
- Marjanovic, A. M., Pavicic, I., Trosic, I. (2014). Cell oxidation–reduction imbalance after modulated radiofrequency radiation. *Electromagn. Biol. Med. (Published online)*. 13:1–6.
- Marzook, E. A., Abd El Moneim, A. E., Elhadary, A. A. (2014). Protective role of sesame oil against mobile base station-induced oxidative stress. *J. Radiat. Res. Appl. Sci.* 7:1–6.
- Meena, R., Kumari, K., Kumar, J., et al. (2013). Therapeutic approaches of melatonin in microwave radiations-induced oxidative stress-mediated toxicity on male fertility pattern of Wistar rats. *Electromagn. Biol. Med.* 33:81–91.
- Megha, K., Deshmukh, P. S., Banerjee, B. D., et al. (2012). Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats. *Indian J. Exp. Biol.* 50:889–896.
- Meral, I., Mert, H., Mert, N., et al. (2007). Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs. *Brain Res.* 1169: 120–124.
- Motawi, T., Darwish, H., Moustafa, Y., et al. (2014). Biochemical modifications and neuronal damage in brain of young and adult rats after long-term exposure to mobile phone radiations. *Cell Biochem. Biophys.* 70:845–855.
- Moustafa, Y. M., Moustafa, R. M., Belacy, A., et al. (2001). Effects of acute exposure to the radiofrequency fields of cellular phones on plasma lipid peroxide and antioxidant activities in human erythrocytes. *J. Pharm. Biomed. Anal.* 26:605–608.
- Nagata, M. (2005). Inflammatory cells and oxygen radicals. *Curr. Drug Targets* 4:503–504.
- Naziroglu, M., Celik, O., Ozgul, C., et al. (2012a). Melatonin modulates wireless (2.45 GHz)-induced oxidative injury through TRPM2 and voltage gated Ca(2+) channels in brain and dorsal root ganglion in rat. *Physiol. Behav.* 105:683–692.
- Naziroglu, M., Cig, B., Dogan, S., et al. (2012b). 2.45-Gz wireless devices induce oxidative stress and proliferation through cytosolic Ca(2+)(+) influx in human leukemia cancer cells. *Int. J. Radiat. Biol.* 88:449–456.
- Naziroglu, M., Gumral, N. (2009). Modulator effects of L-carnitine and selenium on wireless devices (2.45 GHz)-induced oxidative stress and electroencephalography records in brain of rat. *Int. J. Radiat. Biol.* 85: 680–689.
- Nguyen, H. L., Zucker, S., Zarrabi, K., et al. (2011). Oxidative stress and prostate cancer progression are elicited by membrane-type 1 matrix metalloproteinase. *Mol. Cancer Res.* 9:1305–1318.
- Ni, S., Yu, Y., Zhang, Y., et al. (2013). Study of oxidative stress in human lens epithelial cells exposed to 1.8 GHz radiofrequency fields. *PLoS One.* 8:e72370.
- Okayama, Y. (2005). Oxidative stress in allergic and inflammatory skin diseases. *Curr. Drug Targets* 4:517–519.
- Oksay, T., Naziroglu, M., Dogan, S., et al. (2014). Protective effects of melatonin against oxidative injury in rat testis induced by wireless (2.45 GHz) devices. *Andrologia* 46:65–72.
- Oktem, F., Ozguner, F., Mollaoglu, H., et al. (2005). Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone: Protection by melatonin. *Arch. Med. Res.* 36:350–355.
- Oral, B., Guney, M., Ozguner, F., et al. (2006). Endometrial apoptosis induced by a 900-MHz mobile phone: Preventive effects of vitamins E and C. *Adv. Ther.* 23:957–973.
- Oshino, N., Jamieson, D., Sugano, T., et al. (1975). Optical measurement of catalase-hydrogen peroxide intermediate (compound-i) in liver of anesthetized rats and its implication to hydrogen-peroxide production in situ. *Biochem. J.* 146:67–77.
- Ott, M., Gogvadze, V., Orrenius, S., et al. (2007). Mitochondria, oxidative stress and cell death. *Apoptosis* 12:913–922.
- Ozguner, F., Altinbas, A., Ozyaydin, M., et al. (2005a). Mobile phone-induced myocardial oxidative stress: Protection by a novel antioxidant agent caffeic acid phenethyl ester. *Toxicol. Ind. Health.* 21:223–230.
- Ozguner, F., Bardak, Y., Comlekci, S. (2006). Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: A comparative study. *Mol. Cell Biochem.* 282:83–88.
- Ozguner, F., Oktem, F., Ayata, A., et al. (2005b). A novel antioxidant agent caffeic acid phenethyl ester prevents long-term mobile phone exposure-induced renal impairment in rat. Prognostic value of malondialdehyde, N-acetyl-beta-D-glucosaminidase and nitric oxide determination. *Mol. Cell Biochem.* 277:73–80.
- Ozguner, E., Guler, G., Seyhan, N. (2010). Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants N-acetyl cysteine and epigallocatechin-gallate. *Int. J. Radiat. Biol.* 86: 935–945.
- Ozguner, E., Kismali, G., Guler, G., et al. (2013). Effects of prenatal and postnatal exposure to gsm-like radiofrequency on blood chemistry and oxidative stress in infant rabbits, an experimental study. *Cell Biochem. Biophys.* 67:743–751.
- Özorak, A., Naziroglu, M., Çelik, Ö., et al. (2013). Wi-Fi (2.45 GHz)- and mobile phone (900 and 1800 MHz)-induced risks on oxidative stress and elements in kidney and testis of rats during pregnancy and the development of offspring. *Biol. Trace Elem. Res.* 156: 221–229.
- Panagopoulos, D. J., Karabarbounis, A., Margaritis, L. H. (2002). Mechanism for action of electromagnetic fields on cells. *Biochem. Biophys. Res. Commun.* 298:95–102.
- Panagopoulos, D. J., Messini, N., Karabarbounis, A., et al. (2000). A mechanism for action of oscillating electric fields on cells. *Biochem. Biophys. Res. Commun.* 272:634–640.
- Paulraj, R., Behari, J., Rao, A. R. (1999). Effect of amplitude modulated RF radiation on calcium ion efflux and ODC activity in chronically exposed rat brain. *Indian J. Biochem. Biophys.* 36:337–340.
- Pavicic, I., Trosic, I. (2010). Interaction of GSM modulated RF radiation and macromolecular cytoskeleton structures. *Paper presented at the 6th International Workshop on Biological Effects of Electromagnetic Fields.*
- Pilla, A. A. (2012). Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. *Biochem. Biophys. Res. Commun.* 426:330–333.
- Qin, F., Yuan, H., Nie, J., et al. (2014). [Effects of nano-selenium on cognition performance of mice exposed in 1800 MHz radiofrequency fields]. *Wei sheng yan jiu = J. Hygiene Res.* 43:16–21.
- Ragy, M. M. (2014). Effect of exposure and withdrawal of 900-MHz-electromagnetic waves on brain, kidney and liver oxidative stress and some biochemical parameters in male rats. *Electromagn. Biol. Med. (Published online)*:1–6.
- Ralph, S. J., Rodríguez-Enríquez, S., Neuzil, J., et al. (2010). The causes of cancer revisited: “Mitochondrial malignancy” and ROS-induced oncogenic transformation – Why mitochondria are targets for cancer therapy. *Mol. Aspects Med.* 31:145–170.



- Rao, V. S., Titushkin, I. A., Moros, E. G., et al. (2008). Nonthermal effects of radiofrequency-field exposure on calcium dynamics in stem cell-derived neuronal cells: Elucidation of calcium pathways. *Radiat. Res.* 169:319–329.
- Repacholi, M. H., Basten, A., Gebiski, V., et al. (1997). Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. *Radiat. Res.* 147:631–640.
- Ruediger, H. W. (2009). Genotoxic effects of radiofrequency electromagnetic fields. *Pathophysiology* 16:89–102.
- Sadetzki, S., Chetrit, A., Jarus-Hakak, A., et al. (2008). Cellular phone use and risk of benign and malignant parotid gland tumors – A nationwide case-control study. *Am. J. Epidemiol.* 167:457–467.
- Saikhedkar, N., Bhatnagar, M., Jain, A., et al. (2014). Effects of mobile phone radiation (900 MHz radiofrequency) on structure and functions of rat brain. *Neurol. Res.* 36:1072–1079.
- Santini, R., Santini, P., Danze, J. M., et al. (2002). Study of the health of people living in the vicinity of mobile phone base stations: 1. Influences of distance and sex. *Pathol. Biol.* 50:369–373.
- Sato, Y., Akiba, S., Kubo, O., et al. (2011). A case-case study of mobile phone use and acoustic neuroma risk in Japan. *Bioelectromagnetics* 32:85–93.
- Sefidbakht, Y., Moosavi-Movahedi, A. A., Hosseinkhani, S., et al. (2014). Effects of 940 MHz EMF on bioluminescence and oxidative response of stable luciferase producing HEK cells. *Photochem. Photobiol. Sci.* 13:1082–1092.
- Shahin, S., Singh, V. P., Shukla, R. K., et al. (2013). 2.45 GHz microwave irradiation-induced oxidative stress affects implantation or pregnancy in mice, *Mus musculus*. *Appl. Biochem. Biotechnol.* 169:1727–1751.
- Sharma, V. P., Singh, H. P., Kohli, R. K., et al. (2009). Mobile phone radiation inhibits *Vigna radiata* (mung bean) root growth by inducing oxidative stress. *Sci. Total Environ.* 407:5543–5547.
- Sies, H. (2014). Role of metabolic H<sub>2</sub>O<sub>2</sub> generation: Redox signalling and oxidative stress. *J. Biol. Chem.* 289:8735–8741.
- Singh, H. P., Sharma, V. P., Batish, D. R., et al. (2012). Cell phone electromagnetic field radiations affect rhizogenesis through impairment of biochemical processes. *Environ. Monitor. Assess.* 184: 1813–1821.
- Sokolovic, D., Djindjic, B., Nikolic, J., et al. (2008). Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. *J. Radiat. Res. (Tokyo)*. 49: 579–586.
- Sokolovic, D., Djordjevic, B., Kocic, G., et al. (2013). Melatonin protects rat thymus against oxidative stress caused by exposure to microwaves and modulates proliferation/apoptosis of thymocytes. *Gen. Physiol. Biophys.* 32:79–90.
- Suleyman, D., M. Zulkuf, A., Feyzan, A., et al. (2004). Does 900 MHz GSM mobile phone exposure affect rat brain? *Electromagn. Biol. Med.* 23:201–214.
- Szmigielski, S., Szudzinski, A., Pietraszek, A., et al. (1982). Accelerated development of spontaneous and benzopyrene-induced skin cancer in mice exposed to 2450-MHz microwave radiation. *Bioelectromagnetics* 3:179–191.
- Tice, R. R., Hook, G. G., Donner, M., et al. (2002). Genotoxicity of radiofrequency signals. I. Investigation of DNA damage and micronuclei induction in cultured human blood cells. *Bioelectromagnetics* 23:113–126.
- Tkalec, M., Malaric, K., Pevalak-Kozlina, B. (2007). Exposure to radiofrequency radiation induces oxidative stress in duckweed Lemna minor L. *Sci. Total Environ.* 388:78–89.
- Tkalec, M., Stambuk, A., Srut, M., et al. (2013). Oxidative and genotoxic effects of 900 MHz electromagnetic fields in the earthworm *Eisenia fetida*. *Ecotoxicol. Environ. Saf.* 90:7–12.
- Tök, L., Nazıroğlu, M., Doğan, S., et al. (2014). Effects of melatonin on Wi-Fi-induced oxidative stress in lens of rats. *Indian J. Ophthalmol.* 62:12–15.
- Toler, J. C., Shelton, W. W., Frei, M. R., et al. (1997). Long-term, low-level exposure of mice prone to mammary tumors to 435 MHz radiofrequency radiation. *Radiat. Res.* 148:227–234.
- Tomruk, A., Guler, G., Dincel, A. S. (2010). The influence of 1800 MHz GSM-like signals on hepatic oxidative DNA and lipid damage in nonpregnant, pregnant, and newly born rabbits. *Cell. Biochem. Biophys.* 56:39–47.
- Tsybulin, O., Sidorik, E., Brieieva, O., et al. (2013). GSM 900 MHz cellular phone radiation can either stimulate or depress early embryogenesis in Japanese quails depending on the duration of exposure. *Int. J. Radiat. Biol.* 89:756–763.
- Tsybulin, O., Sidorik, E., Kyrlyenko, S., et al. (2012). GSM 900 MHz microwave radiation affects embryo development of Japanese quails. *Electromagn. Biol. Med.* 31:75–86.
- Türedi, S., Hancı, H., Topal, Z., et al. (2014). The effects of prenatal exposure to a 900-MHz electromagnetic field on the 21-day-old male rat heart. *Electromagn. Biol. Med. (Published online)*.1–8.
- Turker, Y., Nazıroglu, M., Gumral, N., et al. (2011). Selenium and L-carnitine reduce oxidative stress in the heart of rat induced by 2.45-GHz radiation from wireless devices. *Biol. Trace Elem. Res.* 143: 1640–1650.
- Vaks, V. L., Domrachev, G. A., Rodygin, Y. L., et al. (1994). Dissociation of water by microwave radiation. *Radiophys. Quant. Electron.* 37:85–88.
- Valko, M., Leibfritz, D., Moncol, J., et al. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.* 39:44–84.
- Valko, M., Rhodes, C. J., Moncol, J., et al. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem. Biol. Interact.* 160:1–40.
- Wang, X., Sharma, R. K., Gupta, A., et al. (2003). Alterations in mitochondria membrane potential and oxidative stress in infertile men: A prospective observational study. *Fertil. Steril.* 80:844–850.
- Wolf, R., Wolf, D. (2007). Increased incidence of cancer near a cell-phone transmitted station. In F. Columbus (Ed.), *Trends in Cancer Prevention* New York: Nova Science Publishers, Inc. pp. 1–8.
- Xu, S., Zhou, Z., Zhang, L., et al. (2010). Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons. *Brain. Res.* 1311:189–196.
- Yakymenko, I., Sidorik, E., Kyrlyenko, S., et al. (2011). Long-term exposure to microwave radiation provokes cancer growth: Evidences from radars and mobile communication systems. *Exp. Oncol.* 33: 62–70.
- Yakymenko, I., Sidorik, E., Tsybulin, O., et al. (2011). Potential risks of microwaves from mobile phones for youth health. *Environ. Health* 56: 48–51.
- Yurekli, A. I., Ozkan, M., Kalkan, T., et al. (2006). GSM base station electromagnetic radiation and oxidative stress in rats. *Electromagn. Biol. Med.* 25:177–188.
- Zhao, T. Y., Zou, S. P., Knapp, P. E. (2007). Exposure to cell phone radiation up-regulates apoptosis genes in primary cultures of neurons and astrocytes. *Neurosci. Lett.* 412:34–38.
- Zmyślony, M., Politanski, P., Rajkowska, E., et al. (2004). Acute exposure to 930 MHz CW electromagnetic radiation in vitro affects reactive oxygen species level in rat lymphocytes treated by iron ions. *Bioelectromagnetics* 25:324–328.
- Zotti-Martelli, L., Peccatori, M., Maggini, V., et al. (2005). Individual responsiveness to induction of micronuclei in human lymphocytes after exposure in vitro to 1800-MHz microwave radiation. *Mutat. Res.* 582:42–52.

Mechanisms of Harm; Blood Brain Barrier; Increased Blood–Brain Barrier Permeability in Mammalian Brain 7 days After Exposure to the Radiation from a GSM-900 Mobile Phone. Pathophysiology (Nittby, Salford et al); 2009



# Increased blood–brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone

Henrietta Nittby<sup>a,\*</sup>, Arne Brun<sup>b</sup>, Jacob Eberhardt<sup>c</sup>, Lars Malmgren<sup>d</sup>,  
 Bertil R.R. Persson<sup>c</sup>, Leif G. Salford<sup>a</sup>

<sup>a</sup> Department of Neurosurgery, Lund University, The Rausing Laboratory and Lund University Hospital, S-22185, Lund, Sweden

<sup>b</sup> Department of Neuropathology, Lund University, The Rausing Laboratory and Lund University Hospital, S-22185, Lund, Sweden

<sup>c</sup> Department of Medical Radiation Physics, Lund University, The Rausing Laboratory and Lund University Hospital, S-22185, Lund, Sweden

<sup>d</sup> The MAX Laboratory, Lund University, The Rausing Laboratory and Lund University Hospital, S-22185, Lund, Sweden

Received 17 December 2008; accepted 30 January 2009

## Abstract

Microwaves were for the first time produced by humans in 1886 when radio waves were broadcasted and received. Until then microwaves had only existed as a part of the cosmic background radiation since the birth of universe. By the following utilization of microwaves in telegraph communication, radars, television and above all, in the modern mobile phone technology, mankind is today exposed to microwaves at a level up to  $10^{20}$  times the original background radiation since the birth of universe.

Our group has earlier shown that the electromagnetic radiation emitted by mobile phones alters the permeability of the blood–brain barrier (BBB), resulting in albumin extravasation immediately and 14 days after 2 h of exposure.

In the background section of this report, we present a thorough review of the literature on the demonstrated effects (or lack of effects) of microwave exposure upon the BBB.

Furthermore, we have continued our own studies by investigating the effects of GSM mobile phone radiation upon the blood–brain barrier permeability of rats 7 days after one occasion of 2 h of exposure. Forty-eight rats were exposed in TEM-cells for 2 h at non-thermal specific absorption rates (SARs) of 0 mW/kg, 0.12 mW/kg, 1.2 mW/kg, 12 mW/kg and 120 mW/kg. Albumin extravasation over the BBB, neuronal albumin uptake and neuronal damage were assessed.

Albumin extravasation was enhanced in the mobile phone exposed rats as compared to sham controls after this 7-day recovery period (Fisher's exact probability test,  $p = 0.04$  and Kruskal–Wallis,  $p = 0.012$ ), at the SAR-value of 12 mW/kg (Mann–Whitney,  $p = 0.007$ ) and with a trend of increased albumin extravasation also at the SAR-values of 0.12 mW/kg and 120 mW/kg. There was a low, but significant correlation between the exposure level (SAR-value) and occurrence of focal albumin extravasation ( $r_s = 0.33$ ;  $p = 0.04$ ).

The present findings are in agreement with our earlier studies where we have seen increased BBB permeability immediately and 14 days after exposure. We here discuss the present findings as well as the previous results of altered BBB permeability from our and other laboratories. © 2009 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Albumin; Blood–brain barrier; Mobile phone; Rat

## 1. Introduction: radiofrequency radiation and the blood–brain barrier

Today about half of the world's population owns the microwave-producing mobile phones. An even larger number is exposed to the radiation emitted from these devices through “passive mobile phoning” [1]. Life-long exposure to the microwaves (MWs) from mobile phones, with start already at a young age, is becoming increasingly common

**Abbreviations:** BBB, blood–brain barrier; CNS, central nervous system; CW, continuous wave; EMF, electromagnetic field; GSM, global system for mobile communication; ICNIRP, International Commission of Non-ionizing Radiation Protection; MRI, magnetic resonance imaging; RF, radio frequency; SAR, specific absorption rate; TEM-cell, transverse electromagnetic transmission line chamber.

\* Corresponding author. Tel.: +46 46 173922; fax: +46 46 188150.

E-mail address: [henrietta.nittby@med.lu.se](mailto:henrietta.nittby@med.lu.se) (H. Nittby).

among the new generations of mobile phone users. The question is: to what extent are living organisms affected by these radio frequency (RF) fields?

The mobile phones are held in close proximity to the head, or within a metre of the head when hands-free sets are used. The emitted microwaves have been shown to have many effects upon the mammalian brain; e.g. alterations of cognitive functions [2,3], changes of neurotransmitter levels such as decrease of cholinergic activity [4], gene expression alterations in cerebellum [5], cortex and hippocampus [6], and impact upon the brain EEG activity [7]. Also, the human brain EEG beta rhythms energies were increased by exposure to 450 MHz MWs modulated at different low frequencies [8]. Recent epidemiological studies also indicate that long-term exposure increases the risk of not only for benign vestibular schwannoma (previously named acoustic neurinoma) [9], but also malignant glioblastoma multiforme [10] for mobile phone use longer than 10 years and with cumulative exposure from mobile phones exceeding 2000 h.

It has been shown that electromagnetic fields (EMFs) increase the permeability of the blood–brain barrier (BBB) (for reference see [11]). The BBB is a hydrophobic barrier, formed by vascular endothelial cells of the capillaries in the brain, with tight junctions between these endothelial cells. It protects the mammalian brain from potentially harmful compounds in the blood. Also, perivascular structures such as astrocytes and pericytes as well as a bi-layered basal membrane help maintaining the BBB.

The current recommendations for limits of exposure to the general public for EMF radiation [12] are set in order to avoid thermal effects upon the brain parenchyma.

In our previous studies we have seen that non-thermal RF fields cause significantly increased leakage of the rats' own albumin through the BBB of exposed rats sacrificed immediately after the exposure, as compared to sham exposed control animals [11,13–18]. Two hours of exposure to the radiation from a global system for mobile communications (GSM) phone at 915 MHz, at non-thermal specific absorption rates (SAR) values of 0.12 mW/kg, 12 mW/kg and 120 mW/kg, gives rise to focal albumin extravasation and albumin uptake into neurons also 14 days after exposure, but not after 28 days [19]. Significant neuronal damage is present 28 days [19] and 50 days after exposure [20], but not after 14 days [19]. Also, in experiments from other laboratories, BBB permeability is increased in connection to mobile phone exposure [21–23] and other kinds of EMF such as magnetic resonance imaging (MRI) exposure [24–26]. In other studies, no such BBB alterations have been demonstrated in connection to mobile phone exposure [27–29] or other kinds of EMF exposure [30,31].

### 1.1. The blood–brain barrier

An intact BBB is necessary for the protection of the mammalian brain from potentially harmful substances circulating in the blood. In the normal brain, the passage of compounds over the BBB is highly restricted and homeostasis within

the sensitive environment of the brain parenchyma can be maintained.

The BBB is formed by the vascular endothelial cells of the capillaries of the brain and the glial cells wrapped around them. The tight junctions, that seal the endothelial cells together, limit paracellular leakage of molecules. A bi-layered basal membrane supports the abluminal side of the endothelial cells. The glial astrocytes, surrounding the surface of the basal membrane cells, are important for the maintenance, functional regulation and repair of the BBB. The protrusions of the astrocytes, called end feet, cover the basal membrane on the outer endothelial surface and thus form a second barrier to hydrophilic molecules and connect the endothelium to the neurons. Twenty-five per cent of the abluminal membrane of the capillary surface is covered by pericytes [32], which are a type of macrophages. Seemingly, they are in the position to significantly contribute to the central nervous system (CNS) immune mechanisms [33].

The physiological properties of the CNS microvasculature are different from those of peripheral organs. The numbers of pinocytotic vesicles for nutrient transport through the endothelial cytoplasm are low and there are no fenestrations. Also, there is a fivefold higher number of mitochondria in the BBB endothelial cells as compared to muscular endothelial cells [34].

In a functioning BBB, the membrane properties control the bidirectional exchange between the general circulation and the CNS. Water, most lipid-soluble molecules, oxygen and carbon dioxide can diffuse from the blood to the nerve cells. The barrier is slightly permeable to ions such as sodium, potassium and chloride, but large molecules, such as proteins and most water-soluble chemicals only pass poorly. However, when this barrier is damaged, in conditions such as tumours, infarcts or infections, also the normally excluded molecules can pass through, possibly bringing toxic molecules out into the brain tissue. The selective permeability is disrupted temporally in cases of epileptic seizures [35,36] and severe hypertension [37]. The result of this can be cerebral oedema, increased intracranial pressure and irreversible brain damage. Also, toxic substances from the blood circulation now reach out to the neurons. Even transient openings of the BBB can lead to permanent tissue damage [37].

### 1.2. The earliest studies on the effects of microwave exposure

The first studies on the MW effects upon the BBB were reported in the 1970s, when the radiation from radars and MW ovens were considered to be possible health threats. Increased leakage of fluorescein after 30 min of pulsed and CW exposure [38] and passage of  $^{14}\text{C}$ -mannitol, inulin and dextran at very low energy levels [39] were reported. The permeation of mannitol was found to be a definite function of exposure parameters such as power density, pulse width, and the number of pulses per second. Also, the BBB permeability depended on the time between the EMF exposure and the

sacrifice of the animals, with more pronounced effects seen in the animals sacrificed earlier after the EMF exposure. In attempts to replicate the findings of Oscar and Hawkins [39], however, these results were not found [40,41]. Similar lack of MW induced BBB effects, was reported by Ward et al. [42] after exposure of rats to CWs at 2450 MHz; Ward and Ali [43] after exposure at 1.7 GHz; and Gruenau et al. [44] after exposure to pulsed or CW waves at 1.8 GHz (including totally 31 rats). On the other hand, Albert and Kerns [45] observed EMF-induced BBB permeability after exposure at 2450 MHz CWs, with an increase in the number of pinocytotic vesicles among the irradiated animals, but after a recovery time of 1–2 h, the permeation was hardly detectable anymore. For details concerning the EMF exposure parameters in these studies, see [11].

### 1.3. MRI exposure

MRI entails a concurrent exposure to a high-intensity static field, a RF field and a time-varying magnetic field. In connection to the introduction of the MRI technique, the effects of exposure to these kinds of fields upon the BBB permeability were investigated.

As mentioned above, Shivers et al. [24] observed that the EMF exposure of the type emitted during a MRI procedure resulted in a temporarily increased BBB permeability in the brains of rats. Through transendothelial channels, a vesicle-mediated transport of horseradish peroxidase (HRP) took place. Replications of the initial findings by Shivers et al. [24] were made by Garber et al. [46], whereas Adzamlı et al. [30] and Preston et al. [31] could not repeat the findings.

After some years, quantitative support of the findings by Shivers et al. [24] was presented by the same group [25,26]. In rats exposed to the MRI, the BBB permeability to DTPA (diethylenetriaminepentaacetic acid) increased. A suggested mechanism explaining the increased permeability was a stimulation of endocytosis, made possible through the time-varying magnetic fields.

Also our studies supported the findings of the Shiver–Prato group; seeing that BBB permeability to albumin was increased after exposure to MRI radiation [13]. The most significant effect was observed after exposure to the RF part of the MRI.

### 1.4. Studies on mobile phone exposure

The mobile phone induced effects upon the BBB permeability is a topic of importance for the whole society today. We have previously found an increased BBB permeability immediately after 2 h of mobile phone exposure [14], and also after 14 days [19] and 50 days [20].

Repetitions of our findings of increased BBB permeability after mobile phone exposure have been made [47,21,22]. Four hours of GSM-900 MHz exposure at brain power densities ranging from 0.3 to 7.5 W/kg resulted in significantly increased albumin extravasation both at the SAR-value of

7.5 W/kg, which is a thermal effect, but also at 0.3 W/kg and 1.3 W/kg [47] (statistical evaluations discussed by Salford et al. [1]). Albumin extravasation was also seen in rats exposed for 2 h to GSM-900 MHz at non-thermal SAR-values of 0.12, 0.5 and 2 W/kg using fluorescein-labelled proteins [21,22]. At SAR of 2 W/kg a marked BBB permeabilization was observed, but also at the lower SAR-value of 0.5 W/kg, permeabilization was present around intracranial blood vessels. However, the extravasation at 0.5 W/kg was seen at a lesser extent as compared to that seen at 2 W/kg. Subgroups of the rats included in these studies were sympathectomised, which means that they were in a chronic inflammation-prone state with increased BBB opening due to changes in the structures of the blood vessels. Interestingly, the sympathectomised rats exposed to GSM radiation had a remarkable increase of the BBB leakage as compared to their sympathectomised sham controls. From these findings it seems likely that an already disrupted BBB is more sensitive to the RF fields than an intact BBB.

In another study, the uptake of rhodamine–ferritin complex through the BBB was investigated [23]. In this study, increased BBB permeability was clearly seen at exposure levels of 2 W/kg and durations of 30–120 min. When the rats were pre-treated with colchicine, the EMF-induced rhodamine–ferritin uptake was however blocked. Colchicine is well-known for its inhibition of microtubular function. It was concluded that the microtubules seemed to play an important role for the BBB opening.

Lack of EMF-induced BBB alterations has also been reported [27–29,48]. In a small study including only 12 EMF exposed animals, no albumin extravasation was seen, neither after 2 nor 4 weeks of 1 h of daily exposure (average whole-body exposure at 0.25 W/kg) [27]. In a study including 40 animals, Kuribayashi et al. [28] concluded no BBB alterations was seen after 90 min of daily EMF exposure for 1–2 weeks at SAR-values of 2 or 6 W/kg. Finnie et al. [29] exposed mice for 1 h daily. However, only the SAR-value of 4 W/kg, which is above the ICNIRP limit [12], was included. In a further study by Finnie et al. [48] 207 mice were exposed for 104 weeks at SAR-values of 0.25–4 W/kg, however without any observable effects upon the BBB permeability. The same group also reported that the immature BBB was insensitive to mobile phone exposure, seen after GSM-900 radiation exposure of pregnant mice from day 1 to day 19 of gestation (SAR of 4 W/kg, exposure for 60 min daily). No increased albumin extravasation was seen in the new-born mice immediately after parturition [49] and the same lack of GSM-900 radiation effects upon the BBB permeability was reported for young rats by Kumlin et al. [50], however, in this case only 12 out of totally 48 exposed rats were analyzed histopathologically. The remaining rats were subject to memory tests, where an improved learning and memory was seen in the EMF exposed rats as compared to the sham controls. Notably, in all these studies, the SAR-values for exposure are relatively high; never including the low SAR-values below 200 mW/kg.



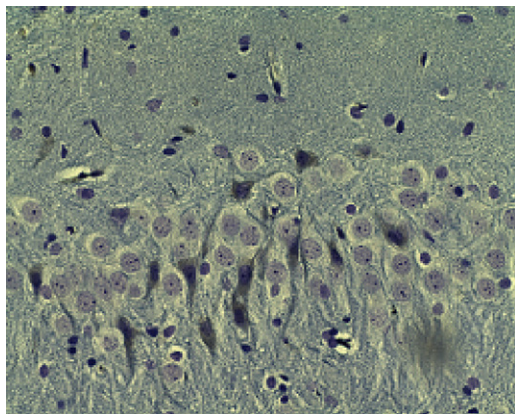


Fig. 1. Albumin neuronal uptake and early neuronopathy in the hippocampal pyramidal cell row among normal neurons. Albumin: cresyl violet,  $\times 20$ .

In more recent years, *in vitro* models have been increasingly applied to investigate the BBB; in one of these, it was shown that EMFs at 1.8 GHz increase the permeability to sucrose [51]. After modifications of the BBB model to one with higher tightness, however, the same group could not replicate their initial findings [52]. With application of the EMF of the kind emitted from 3G mobile phones, the same group further concluded that their *in vitro* BBB model also did not alter its tightness or transport behaviour in connection to this type of exposure [53].

#### 1.5. Neuronal damage in connection to mobile phone exposure

In our previous studies of animals surviving a longer period after the exposure, we have evaluated the occurrence of neuronal damage extensively [19,20]. This neuronal damage is seen as condensed dark neurons. Dark neurons have been proposed to have three main characteristics [54]: (i) irregular cellular outlines, (ii) increased chromatin density in the nucleus and cytoplasm and (iii) intensely and homogeneously stained nucleus. Twenty-eight days after 2 h of mobile phone exposure, the neuronal damage was significantly increased in the exposed rats as compared to the sham exposed controls [19]. Also 50 days after the same kind of mobile phone exposure, there was an increased occurrence of neuronal damage [20].

In our studies, normal neurons have been shown to have increased uptake of albumin [19] (Fig. 1). Also, in dark neurons this neuronal albumin uptake can be seen (Fig. 2). In our previous studies, damaged neurons were seen in all locations, intermingled with normal neurons especially in the cortex, hippocampus and basal ganglia. The damaged neurons were often shrunken and dark staining, homogenized with loss of discernable internal cell structures (Fig. 3). Some damaged neurons showed microvacuoles in the cytoplasm (Fig. 4). These vacuoles are a sign of severe neuronopathy, indicating an active pathological process. There was no evidence of haemorrhages or glial reaction.

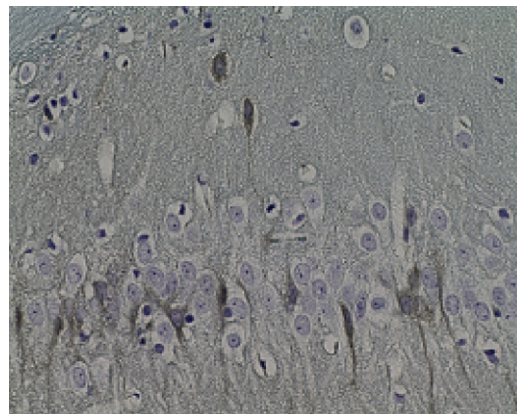


Fig. 2. Shrunken homogenized dark neurons with brownish discoloration due to uptake of albumin, interspersed among normal neurons in the hippocampal pyramidal cell row. Albumin: cresyl violet,  $\times 20$ . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

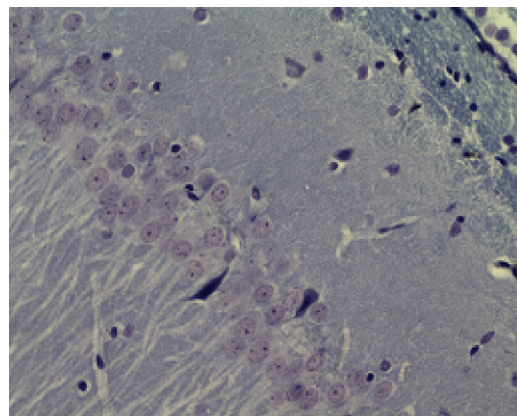


Fig. 3. Two dark neurons in the hippocampal pyramidal cell row. Albumin: cresyl violet,  $\times 20$ .

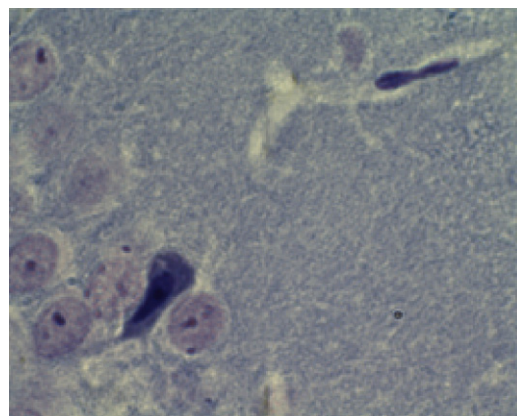


Fig. 4. Dark neuron in the hippocampal pyramidal cell row, with homogenized nucleus and cytoplasm with a vacuole. Higher magnification of part of the figure. Albumin: cresyl violet,  $\times 40$ .



Dark neurons are reported in clinical and experimental neuropathology from living tissues, but not in autopsy material unless the post-mortem period is short. This could indicate that the formation of dark neurons is an active process that requires living neurons and that these cells must be reasonably intact [55]. This could be in accordance with our findings from the 50-days survival animals, where apoptosis could not be detected in any of the RF EMF exposed brains with application of Caspase-3 [56].

Dark neurons occur not only after GSM exposure [19,20] but also in connection to experimental ischemia [57], hypoglycemia [58] and epilepsy [59]. Possibly, dark neurons could be artefacts, having a pressure-derived mechanical origin, as has been shown for cortical biopsies (this is less likely considering the atraumatic method of dissection used here including fixation before handling and in view of the deep location of the dark neurons). However, dark neurons also appear as a result of other, and not fully clarified, mechanisms, as seen in the case of GSM exposure, ischemia, hypoglycemia and epilepsy. A pharmacologic origin, such as depolarization related to tissue glutamate release in injury, could explain the pathogenetic mechanism for dark neurons in these cases, rather than the pressure-derived mechanical origin. Indeed, the formation of dark neurons can be prevented using pharmacologic forms of glutamate antagonism [55]. In the case of our studies, our technique for the resection of the rat brains is chosen to avoid mechanical pressure.

Findings of dark neurons in connection to mobile phone exposure have been reported by Ihan et al. [60] (GSM exposure of rats for 7 days, 1 h daily). Also, an increase of oxidative damage was seen in the exposed rats as a significant increase in malondialdehyde (MDA) (an index for lipid peroxidation), nitric oxide (NO) levels, brain xanthine oxidase (XO) and adenosine deaminase (ADA) activities, as compared to the controls. With treatment of the anti-oxidant *Ginkgo biloba*, the EMF induced increments of XO, ADA, MDA and NO were prevented. The anti-oxidant activity of *G. biloba* is attributed to its flavinoid glycosides, which are the active compounds in the leaves. The action of these flavinoids is to destroy free radicals, such as NO and lipid peroxide radicals. Also the formation of dark neurons was reported to be prevented when the rats had been treated with *G. biloba*. Other attempts to repeat our findings of dark neurons after mobile phone exposure have been performed in a collaborative effort with Bernard Veyret's group in Bordeaux [61]. In this study, the situation 14 days and 50 days after 2 h of GSM-900 radiation exposure at average brain SAR-values of 0.14 W/kg and 2.0 W/kg was evaluated. No increased amount of dark neurons was reported.

It has been suggested that BBB leakage is the major reason for nerve cell injury, such as dark neurons in stroke-prone spontaneously hypertensive rats [62]. Albumin leaks into the brain and neuronal degeneration is seen in areas with BBB disruption in several circumstances: after intracarotid infusion of hyperosmolar solutions in rats [63]; in the stroke prone hypertensive rat [65]; in acute hypertension by aor-

tic compression in rats [37]. The linkage between albumin extravasation over the BBB and neural damage might be a potentiating effect of albumin upon the glutamate-mediated neurotoxicity [64]. Indeed, both albumin- and glutamate-induced lesions have the same histopathological appearance with invasion of macrophages and absence of neuronal cell bodies and axons in the lesion areas [65]. The glutamate itself can also increase the BBB opening [66], leading to further albumin extravasation out into the brain parenchyma. From our previous findings of albumin extravasation 14 days after exposure [19] and dark neurons not until after 28 days [19] and 50 days [20], it could be hypothesized that albumin extravasation into the brain parenchyma, is the first observable effect of the mobile phone exposure. The albumin leakage precedes and possibly could be the cause of, the damage to the neurons seen as the dark neurons later on. In this connection, the findings of [37] that transient openings of the BBB can result in permanent tissue damage, can also be mentioned. Hypertensive opening of the BBB resulted in albumin extravasation after 2 h, but the effects remained, although to a lesser extent, also after 7 days. Many neurons with cytoplasmatic immunoreactivity for albumin appeared shrunken. Seven days after the BBB opening, there was a neuronal loss in these areas and a vigorous glial reaction, indicating that some neurons were irreversibly damaged [37].

## 2. Aims of the present study

In the present study we have continued to investigate the effects of EMFs upon the rat brain, now with focus on what happens 7 days after GSM exposure at 915 MHz for 2 h at non-thermal energy levels of 0.12 mW/kg, 1.2 mW/kg, 12 mW/kg and 120 mW/kg. The main questions to be answered were: whether the same increase of the BBB permeability is seen 7 days after exposure as that showed previously immediately after exposure and after 14 days, and whether different exposure levels result in a different response.

In order to compare to our previous findings, we have used the same exposure system, GSM signal, animal model and histopathological methods as in our previous studies.

## 3. Materials and methods

### 3.1. GSM exposure

The animals were exposed to RF EMFs in the same transverse electromagnetic transmission line cell (TEM-cells) as previously described and used by [1,2,5,13–19]. The TEM-cells were designed by dimensional scaling from previously constructed cells at the National Bureau of Standards [67]. TEM-cells are known to generate uniform EMFs for standard measurements.

A genuine GSM mobile phone, operating at the 900 MHz frequency band, with programmable power output, was con-

nected via a coaxial cable to the TEM-cells. Through a power splitter, the power was divided into equal parts fed into the four TEM-cells used (TEM-cell A, B, C and D). No voice modulation was applied. Each of the four TEM-cells is connected to a 50  $\Omega$  dummy load, into which the output is terminated. By using these TEM-cells, the pulse modulated exposure fields can be accurately generated without the distortion that is typically introduced when conventional antennas are used to establish impulse test fields. Thus, a relatively homogeneous exposure of the animals is allowed [68].

The TEM-cell is enclosed in a wooden box (inner dimensions of 15 cm  $\times$  15 cm  $\times$  15 cm) that supports the outer conductor, made of brass net, and central conducting plate. The central plate separates the top and bottom of the outer conductor symmetrically. Eighteen holes (diameter 18 mm) in the sidewalls and top of the wooden box make ventilation possible. Air is circulated through the holes of the TEM-cells using four fans, each placed next to the outer walls of its respective TEM-cell. The holes are also used for examination of the interior during exposure. For a further description of the TEM-cell, see [68].

The rats were placed in plastic trays (14 cm  $\times$  14 cm  $\times$  7 cm) to avoid contact with the central plate and outer conductor. The bottom of the tray was covered with absorbing paper to collect urine and faeces. Each TEM-cell contained two plastic trays, one above and one below the centre septum. Thus two rats could be kept in each TEM-cell simultaneously. All the animals could move and turn around within the TEM-cells.

For the actual experimental situation with one rat in each compartment of the TEM-cell, the conversion factor  $K$  for SAR per unit of input power could be fitted to the data as

$$K = (1.39 \pm 0.17) - (0.85 \pm 0.22)w \quad (1)$$

with  $w$  the sum of weights in kilograms of the 2 rats in the cell and the variance given as SEM. For a more detailed description, see [2].

Whole-body SAR and brain SAR vary with orientation. In our present set-up, the average of SAR for the brain grey matter was 1.06 times the average whole-body SAR, with a standard deviation of 56% around the average value for the different orientations, as estimated by us previously [19].

### 3.2. Animals

All animal procedures were performed according to the practices of the Swedish Board of Animal Research and were approved by the Animal Ethics Committee, Lund-Malmö.

Forty-eight inbred male and female Fischer 344 rats (the rats were supplied by Scanbur AB, Stockholm, Sweden) were 2–3 months of age at the initiation of the EMF exposure. Male and female rats weighed 225 g  $\pm$  56 g (standard deviation) and 233 g  $\pm$  60 g (standard deviation) respectively.

The rats were housed in rat hutches, two in each cage, under standard conditions of 22 °C room temperature, artificial daylight illumination and rodent chow and tap water *ad libitum*.

The 48 rats were divided into four exposure groups, each group consisting of 8 rats, and one sham exposed group with 16 animals.

The peak power output from the GSM mobile phone fed into the TEM-cells was 1 mW, 10 mW, 100 mW and 1000 mW per cell respectively for a period of 2 h. This resulted in average whole-body SAR of 0.12 mW/kg, 1.2 mW/kg, 12 mW/kg and 120 mW/kg for the four different exposure groups.

All animals were kept in the animal facilities for a recovery period of 7 days after exposure. At the end of this period they were anaesthetized and sacrificed by perfusion-fixation with 4% formaldehyde.

### 3.3. Histopathology and methods

The brains were fixed *in situ* through saline perfusion through the ascending aorta for 3 min followed by 4% formaldehyde for 10 min and immersion in 4% formaldehyde for 24 h. They were then removed from the skulls by a non-traumatic technique (resection of bone structures at the skull base, followed by a midline incision from the foramen magnum to the nose) and immersion fixed in 4% formaldehyde for more than 24 h. Whole coronal sections of the brains were dehydrated and embedded in paraffin, sectioned at 5  $\mu$ m with a microtome and stained for RNA/DNA with cresyl violet to visualize damaged neurons. Albumin was demonstrated with the IgG fraction of rabbit anti-rat albumin (Dakopatts, Helsingborg, Sweden) diluted 1:8,000. This reveals albumin as brownish spotty or more diffuse discolorations. Biotinylated swine anti-rabbit IgG was used as a secondary antibody. Then avidin, peroxidase conjugated, was coupled to the biotin and visualized with DAB (diaminobenzidine).

All brains were examined histopathologically by our neuropathologist (A.B.). All microscopic analyses were performed blind to the test situation.

Regarding albumin extravasation, the number of immunopositive extravasates (foci) were recorded under a microscope. None or occasional minor leakage was rated as normal, whereas one larger or several leakages were regarded as pathological. Immunopositive sites were, however, disregarded when localized in the hypothalamus, above the median eminence and laterally including the lateral hypothalamic nuclei, in the immediate vicinity of the third ventricle and just beneath the pial membrane. These structures are well known for their insufficient BBB. Also the presence and distribution of albumin uptake into neurons was judged semi-quantitatively.

Regarding neuronal damage, this were judged semi-quantitatively as no or occasional (score 0), moderate (score 1) or abundant occurrence (score 2) of dark neurons.

### 3.4. Statistics

As an initial discriminative test, the occurrence of an effect of exposure (score 1 or higher for albumin foci; score 0.5 or higher for neuronal albumin uptake and dark neurons) was tested against sham exposed controls using Fisher's exact probability test.

The Kruskal–Wallis one-way analysis of variance by ranks was used for a simultaneous statistical test of the score distributions for the five conditions of sham or EMF exposure. When the null hypothesis could be rejected, the non-parametric Mann–Whitney *U*-test for independent samples was used to compare each of the groups of GSM exposed and sham exposed animals.

The occurrence of covariates such as gender, the position of the rat in the TEM-cell (upper/lower compartment) and the TEM-cell used (TEM-cell A, B, C or D) was evaluated using linear regression analysis.

Spearman's non-parametric correlation analysis was used for evaluation of correlation between exposure level, albumin foci, neuronal albumin and dark neurons.

## 4. Results

In exposed animals there were albumin positive foci around capillaries in the white and grey matter (Fig. 5). The albumin had diffused into the neuropil between the cell bodies, surrounding the neurons, which either contained no albumin or contained albumin in some foci. Scattered neurons were albumin positive. Regarding the dark neurons, cresyl violet staining showed that these were scattered and sometimes grouped within the brain parenchyma.

The occurrence of albumin outside brain vessels was characterized as albumin foci around vessels. After the 7 days recovery time, albumin foci were found significantly more often among exposed rats (25%) than among sham exposed

rats (0%) (Fisher's exact probability test,  $p = 0.04$ ). There was a low, but significant correlation between the exposure level (SAR-value) and the occurrence of albumin foci (Spearman analysis,  $r_s = 0.33$ ;  $p = 0.04$ ). Taking the level of exposure and quantification of neuropathological effects into account it could be concluded from a simultaneous non-parametric comparison of all 5 exposure levels with the Kruskal–Wallis test, that the distribution of albumin foci differed significantly (Kruskal–Wallis,  $p = 0.012$ ).

Pair-wise comparisons between the different exposure levels and sham exposed animals revealed statistically significant differences for SAR of 12 mW/kg (Mann–Whitney,  $p = 0.007$ ), whereas a trend of increased albumin extravasation could be seen for 0.12 mW/kg (Mann–Whitney,  $p = 0.1$ ) and 120 mW/kg (Mann–Whitney,  $p = 0.1$ ).

Also, the occurrence of neuronal albumin was evaluated. A simultaneous analysis for all exposure levels revealed a significant difference between the five groups (Kruskal–Wallis,  $p = 0.03$ , however Fisher's exact probability,  $p = \text{ns}$ ). A pair-wise comparison revealed that albumin uptake occurred more frequently at 1.2 mW/kg as compared to sham exposed (Mann–Whitney,  $p = 0.02$ ). No difference was found for the occurrence of neuronal damage (Kruskal–Wallis,  $p = \text{ns}$ ; Fisher's exact probability test,  $p = \text{ns}$ ).

Linear regression analysis did not reveal any influence of gender, position of the animals in the TEM-cell (upper/lower compartment) or the TEM-cell used (TEM-cell A, B, C or D) on the frequency of albumin foci, neuronal albumin or occurrence of dark neurons.

## 5. Discussion

The present study provides evidence that GSM exposure results in disruption of the BBB permeability, with remaining, observable effects 7 days after the exposure occasion. Only non-thermal SAR-levels, below the limits of allowed exposure for humans [12] are considered. This finding of increased albumin extravasation after 7 days (Kruskal–Wallis,  $p = 0.012$  with all animals included in the analysis, which is also in agreement with the Fisher's exact probability test,  $p = 0.04$ ) is in line with our earlier findings of albumin leakage both immediately following 2 h of GSM exposure [16] and 14 days [19] after 2 h of GSM exposure. Also, the increased occurrence of neuronal albumin 7 days after the exposure is in line with the findings 14 days after exposure [19].

In our previous study, where the animals have been sacrificed immediately after the EMF exposure, we have seen albumin extravasation only at the most in 50% of the identically exposed animals, although all animals are inbred Fischer 344 rats [16]. Among the rats exposed to the pulse modulated EMFs at 915 MHz, 35% showed albumin extravasation. Also in the sham exposed animals, albumin leakage was present (in 17% of the animals). When the animals have survived 7 days after the EMF exposure, albumin extravasation is seen in a lesser proportion (25% of the exposed

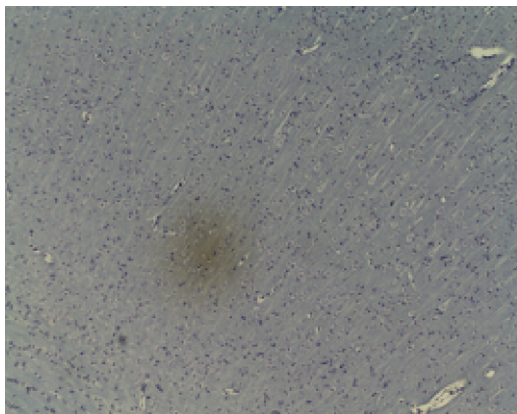


Fig. 5. Focal leakage of albumin shown in brown in the cortex. Albumin: cresyl violet,  $\times 10$ . GSM-900 EMF exposure at 12 mW/kg. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)



animals) and in none of the sham controls. This could be due to a rapid diffusion of extravasated albumin down to, and beyond concentrations possible to demonstrate immunohistochemically. Numerous routes of clearance of extravasated molecules out from the brain tissue are present in the living brain and compounds can also become sequestered intracellularly, become protein bound or metabolized. After 14 days, albumin extravasation is seen in a somewhat larger proportion of the EMF exposed animals (29% of the exposed animals) and none of the sham controls. Thus, a secondary BBB opening might have started at some time point after the initial opening, leading to a vicious circle of albumin leakage.

The mechanism for the passage of albumin over the BBB is not clear. Extravasation might occur through paracellular routes, including alterations of tight junctions between the vascular endothelial cells, or transcellular routes with induction of pinocytosis or transcytosis, formation of transendothelial channels or disruption of the endothelial cell membrane. In connection to EMF exposure, amplified vesicle-mediated transport across the microvessel endothelium occurs, including also transendothelial channels, but no passage through disrupted inter-endothelial tight junctions [24].

One remarkable observation is that exposure at very low whole-body average power densities gives rise to a pronounced albumin leakage. In the present study, significant effects could be seen already at 12 mW/kg, although the different animal groups included a relatively small number of animals. Most certainly, the trends seen for exposure levels of 0.12 mW/kg and 120 mW/kg would have reached statistical significance if more animals had been included in the different exposure groups.

The phenomenon with increased BBB permeability already at very low energy levels might represent a U-curve response. In our other studies, we have seen that the rats in several of the groups with different SAR-levels of EMF exposure have a significant BBB opening [16,19]. The U-response curve occurs also in connection with other kinds of MW exposure, where cerebral vessel permeability after an initial rise decreased with increasing MW power [39].

Further investigation of BBB permeability in connection to EMF exposure is important not only in order to reduce the potentially harmful effects, but also to use possible beneficial effects [69]. The transport of drugs over the BBB might be regulated, so that targets within the brain can be reached. For example, steering of BBB passage of the antiretroviral agent saquinavir has been accomplished in an *in vitro* model of the human BBB, where a frequency of 915 MHz generated the highest BBB permeability [69]. This could be extremely important in order to reduce the HIV replication in the brain of HIV-infected individuals.

## 6. In conclusion

The time between EMF exposure and sacrifice of the animals is of great importance for the detection of albumin foci.

Seven days after 2 h of GSM mobile phone exposure, there is still an increased permeability of the BBB of exposed rats. This is in concordance with earlier findings of albumin extravasation out into the brain parenchyma immediately and 14 days after 2 h of mobile phone exposure.

## 7. General conclusion

Taken together, it can be concluded that in a number of studies MW effects upon the BBB permeability have been observed. Increased permeability can be seen both immediately after exposure, but also 7 days after the exposure, as reported in this primary report, and after 14 days. It seems that the effects of the MW radiation might result in persistent changes, such as those seen in our own studies with neuronal damage both 28 and 50 days after 2 h of mobile phone exposure. In a future perspective, with increasing number of active mobile phone users, passive mobile phoning, radiation emitted from base stations and also MWs emitted from other communication sources, effects of low non-thermal levels of exposure must be considered further. The effects seen in the rat studies give some clues about what might possibly happen in the human brain, with a BBB very similar to that of rats. While awaiting latency periods long enough for adequate epidemiological interpretations, further studies on both animals and cells are of utmost importance.

## Acknowledgements

We thank BMA Susanne Strömblad and BMA Catarina Blennow at the Rausing Laboratory for excellent technical assistance.

This work was supported by a grant from the Hans and Märta Rausing Charitable Foundation.

## References

- [1] L.G. Salford, B. Persson, L. Malmgren, A. Brun, in: P. Marco (Ed.), *Téléphonie Mobile et Barrière Sang-Cerveau. Téléphonie mobile—effets potentiels sur la santé des ondes électromagnétiques de haute fréquence*, Emburg, Belgium, 2001, pp. 141–152.
- [2] H. Nittby, G. Grafström, D. Tian, A. Brun, B.R.R. Persson, L.G. Salford, J. Eberhardt, Cognitive impairment in rats after long-term exposure to GSM-900 mobile phones, *Bioelectromagnetics* 29 (2008) 219–232.
- [3] V. Keetly, A.W. Wood, J. Spong, C. Stough, Neuropsychological sequelae of digital mobile phone exposure in humans, *Neuropsychologia* 44 (2006) 1843–1848.
- [4] H. Lai, M.A. Carino, A. Horita, A.W. Guy, Opioid receptor subtypes that mediate a micro-wave induced decrease in central cholinergic activity in the rat, *Bioelectromagnetics* 13 (1992) 237–246.
- [5] I.Y. Belyaev, C. Bauréus Koch, O. Terenius, K. Roxström-Lindquist, L.O.G. Malmgren, W.H. Sommer, L.G. Salford, B.R.R. Persson, Exposure of rat brain to 915 MHz GSM microwaves induces changes in gene expression but not double stranded DNA breaks or effects on chromatin conformation, *Bioelectromagnetics* 27 (2006) 295–306.

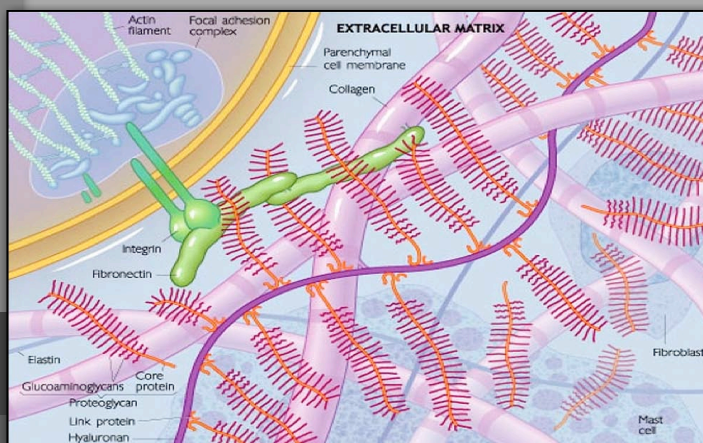
- [6] H. Nittby, B. Widegren, M. Krogh, G. Grafström, G. Rehn, H. Berlin, J.L. Eberhardt, L. Malmgren, B.R.R. Persson, L.G. Salford, Exposure to radiation from global system for mobile communications at 1800 MHz significantly changes gene expression in rat hippocampus and cortex, *Environmentalist* (2008b) (published online ahead of print 15 April 2008).
- [7] F. Vecchio, C. Babilono, F. Ferreri, G. Curcio, R. Fini, C. Del Percio, Maria Rossini P., Mobile phone emission modulated interhemispheric functional coupling of EEG alpha rhythms, *Eur. J. Neurosci.* 25 (2007) 1908–1913.
- [8] H. Hinrikus, M. Bachmann, J. Lass, D. Karai, V. Tuulik, Effect of low frequency modulated microwave exposure on human EEG: individual sensitivity, *Bioelectromagnetics* 29 (2008) 527–538.
- [9] L. Hardell, M. Carlberg, Hansson Mild F.K., Case-control study on cellular and cordless telephones and the risk for acoustic neuroma or meningioma in patients diagnosed 2000–2003, *Neuroepidemiology* 25 (2005) 120–128.
- [10] L. Hardell, M. Carlberg, K. Hansson Mild, Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003, *Int. Arch. Occup. Environ. Health* 79 (2006) 630–639.
- [11] H. Nittby, G. Grafström, J.L. Eberhardt, L. Malmgren, A. Brun, B.R.R. Persson, L.G. Salford, Radiofrequency and extremely low-frequency electromagnetic field effects on the blood-brain barrier, *Electromagn. Biol. Med.* 27 (2008) 103–126.
- [12] ICNIRP, Guidelines for limiting exposure to time-varying electric, magnetic and electromagnetic fields (up to 300 GHz), *Health Phys.* 74 (1998) 494–522.
- [13] L.G. Salford, A. Brun, J. Eberhardt, L. Malmgren, B.B. Persson, Electromagnetic field-induced permeability of the blood-brain barrier shown by immunohistochemical methods. Interaction mechanism of low-level electromagnetic fields, in: B. Nordén, C. Ramel (Eds.), *Living Systems*, Oxford University Press, Oxford, UK, 1992, pp. 251–258.
- [14] L.G. Salford, A. Brun, J.L. Eberhardt, B.R.R. Persson, Permeability of the blood-brain-barrier induced by 915 MHz electromagnetic-radiation continuous wave and modulated at 8, 16, 50 and 200 Hz, *Bioelectrochem. Bioenerg.* 30 (1993) 293–301.
- [15] L.G. Salford, A. Brun, K. Stureson, J.L. Eberhardt, B.R.R. Persson, Permeability of the blood-brain-barrier induced by 915 MHz electromagnetic-radiation continuous wave and modulated at 8, 16, 50 and 200 Hz, *Microsc. Res. Technol.* 27 (1994) 535–542.
- [16] B.R.R. Persson, L.G. Salford, A. Brun, Blood-brain barrier permeability in rats exposed to electromagnetic fields used in wireless communication, *Wireless Networks* 3 (1997) 455–461.
- [17] L.G. Salford, H. Nittby, A. Brun, G. Grafström, J.L. Eberhardt, L. Malmgren, B.R.R. Persson, Non-thermal effects of EMF upon the mammalian brain: the Lund experience, *Environmentalist* 27 (2007) 493–500.
- [18] L.G. Salford, H. Nittby, A. Brun, G. Grafström, L. Malmgren, M. Sommarin, J. Eberhardt, B. Widegren, B.R.R. Persson, The mammalian brain in the electromagnetic fields designed by man—with special reference to blood-brain barrier function, neuronal damage and possible physical mechanisms, *Prog. Theoret. Phys. Suppl.* 174 (2008) 283–309.
- [19] J.L. Eberhardt, B.R. Persson, A.E. Brun, L.G. Salford, L.O. Malmgren, Blood-brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones, *Electromagn. Biol. Med.* 27 (2008) 215–229.
- [20] L.G. Salford, A. Brun, J.L. Eberhardt, L. Malmgren, B.R.R. Persson, Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones, *Environ. Health. Perspect.* 111 (2003) 881–883.
- [21] F. Töre, P.E. Dulou, E. Haro, B. Veyret, P. Aubineau, Two-hour exposure to 2-W/kg 900-MHz GSM microwaves induces plasma protein extravasation in rat brain and dura mater, in: *Proceedings of the 5th International Congress of the EBPA*, Helsinki, Finland, 2001, pp. 43–45.
- [22] F. Töre, P.E. Dulou, E. Haro, B. Veyret, P. Aubineau, Effect of 2 h GSM-900 microwave exposures at 2.0, 0.5 and 0.12 W/kg on plasma protein extravasation in rat brain and dura mater, in: *Proceedings of the 24th Annual Meeting of the BEMS*, 2002, pp. 61–62.
- [23] C. Neubauer, A.M. Phelan, H. Kues, D.G. Lange, Microwave irradiation of rats at 2.45 GHz activates pinocytotic-like uptake of tracer by capillary endothelial cells of cerebral cortex, *Bioelectromagnetics* 11 (1990) 261–268.
- [24] R.R. Shivers, M. Kavaliers, G.C. Teskey, F.S. Prato, R.M. Pelletier, Magnetic resonance imaging temporarily alters BBB permeability in the rat, *Neurosci. Lett.* 76 (1987) 25–31.
- [25] F.S. Prato, R.H. Frappier, R.R. Shivers, M. Kavaliers, P. Zabel, D. Drost, T.Y. Lee, Magnetic resonance imaging increases the BBB permeability to 153-gadolinium diethylenetriaminepentaacetic acid in rats, *Brain Res.* 523 (1990) 301–304.
- [26] F.S. Prato, J.M. Wills, J. Roger, H. Frappier, D.J. Drost, T.Y. Lee, R.R. Shivers, P. Zabel, BBB permeability in rats is altered by exposure to magnetic fields associated with magnetic resonance imaging at 1.5 T, *Microsc. Res. Technol.* 27 (1994) 528–534.
- [27] G. Tsurita, H. Nagawa, S. Ueni, S. Watanabe, M. Taki, Biological and morphological effects on the brain after exposure of rats to a 1439 MHz TDMA field, *Bioelectromagnetics* 21 (2000) 364–371.
- [28] M. Kuribayashi, J. Wang, O. Fujiwara, Y. Doi, K. Nabae, S. Tamano, T. Ogiso, M. Asamoto, T. Shirai, Lack of effects of 1439 MHz electromagnetic near field exposure on the BBB in immature and young rats, *Bioelectromagnetics* 26 (2005) 578–588.
- [29] J.W. Finnie, P.C. Blumbergs, J. Manavis, T.D. Utteridge, V. Gebbski, J.G. Swift, B. Vernon-Roberts, T.R. Kucher, Effect of global system for mobile communication (GSM)-like radiofrequency fields on vascular permeability in mouse brain, *Pathology* 33 (2001) 338–340.
- [30] I.K. Adzamlı, E.A. Jolesz, M. Blau, An assessment of BBB integrity under MRI conditions: brain uptake of radiolabelled Gd-DTPA and In-DTPA-IgG, *J. Nucl. Med.* 30 (1989) 839–840.
- [31] E. Preston, K. Buffler, N. Haas, Does magnetic resonance imaging compromise integrity of the BBB? *Neurosci. Lett.* 101 (1989) 46–50.
- [32] R.N. Frank, S. Dutta, M.A. Mancini, Pericyte coverage is greater in the retinal than in the cerebral capillaries of the rat, *Invest. Ophthalmol. Vis. Sci.* 28 (1987) 1086–1091.
- [33] W.E. Thomas, Brain macrophages: on the role of pericytes and perivascular cells, *Brain. Res. Rev.* 31 (1999) 42–57.
- [34] W.H. Oldendorf, M.E. Cornford, W.J. Brown, The large apparent work capability of the BBB: a study of the mitochondrial content of capillary endothelial cells in brain and other tissues of the rat, *Ann. Neurol.* 1 (1977) 409–417.
- [35] A. Mihály, B. Bozöky, Immunohistochemical localization of serum proteins in the hippocampus of human subjects with partial and generalized epilepsy and epileptiform convulsions, *Acta Neuropathol.* 127 (1984) 251–267.
- [36] A. Mihály, B. Bozöky, Immunohistochemical localization of extravasated serum albumin in the hippocampus of human subjects with partial and generalized and epileptiform convulsions, *Acta Neuropathol.* 65 (1984) 471–477.
- [37] T.E.O. Sokrab, B.B. Johansson, A transient hypertensive opening of the BBB can lead to brain damage, *Acta Neuropathol.* 75 (1988) 557–565.
- [38] A.H. Frey, S.R. Feld, B. Frey, Neural function and behaviour: defining the relationship, *Ann. NY. Acad. Sci.* 247 (1975) 433–439.
- [39] K.J. Oscar, T.D. Hawkins, Microwave alteration of the BBB system of rats, *Brain Res.* 126 (1977) 281–293.
- [40] J.H. Merritt, A.F. Chamness, S.J. Allen, Studies on BBB permeability, *Radial. Environ. Biophys.* 15 (1978) 367–377.
- [41] E. Preston, R.J. Vavasour, H.M. Assenheim, Permeability of the BBB to mannitol in the rat following 2450MHz microwave irradiation, *Brain Res.* 174 (1979) 109–117.
- [42] T.R. Ward, J.A. Elder, M.D. Long, D. Svendsgaard, Measurement of BBB permeation in rats during exposure to 2450-MHz microwaves, *Bioelectromagnetics* 3 (1982) 371–383.

- [43] T.R. Ward, J.S. Ali, BBB permeation in the rat during exposure to low-power 1.7-GHz microwave radiation, *Bioelectromagnetics* 6 (1985) 131–143.
- [44] S.P. Gruenau, K.J. Oscar, M.T. Folker, S.I. Rapoport, Absence of microwave effect on blood–brain-barrier permeability to [C-14]-labeled sucrose in the conscious rat, *Exp. Neurol.* 75 (1982) 299–307.
- [45] E.N. Albert, J.M. Kerns, Reversible microwave effects on the BBB, *Brain Res.* 230 (1981) 153–164.
- [46] H.J. Garber, W.H. Oldendorf, L.D. Braun, R.B. Lufkin, MRI gradient fields increase brain mannitol space, *Magn. Reson. Imag.* 7 (1989) 605–610.
- [47] K. Fritze, C. Sommer, Effect of global system for mobile communication (GSM) microwave exposure on BBB permeability in rat, *Acta Neuropathol.* 94 (1997) 465–470.
- [48] J.W. Finnie, P.C. Blumbergs, J. Manavis, T.D. Utteridge, V. Gebiski, R.A. Davies, B. Vernon-Roberts, T.R. Kuchel, Effect of long-term mobile communication microwave exposure on vascular permeability in mouse brain, *Pathology* 34 (2002) 244–347.
- [49] J.W. Finnie, P.C. Blumbergs, Z. Cai, J. Manavis, T.R. Kuchel, Effect of mobile telephony on blood–brain barrier permeability in the fetal mouse brain, *Pathology* 38 (2006) 63–65.
- [50] T. Kumlin, H. Livonen, P. Miettinen, A. Juvonen, T. van Groen, L. Paranen, R. Pitkäaho, J. Juutilainen, H. Tanila, Mobile phone radiation and the developing brain: behavioral and morphological effects in juvenile rats, *Radiat. Res.* 168 (2007) 471–479.
- [51] A. Schirmacher, S. Winters, S. Fischer, J. Goeke, H.J. Galla, U. Kullnick, E.B. Ringelstein, F. Stögbauer, Electromagnetic fields (1.8 GHz) increase the permeability to sucrose of the BBB in vitro, *Bioelectromagnetics* 21 (2000) 338–345.
- [52] H. Franke, E.B. Ringelstein, F. Stögbauer, Electromagnetic fields (GSM1800) do not alter BBB permeability to sucrose in models in vitro with high barrier tightness, *Bioelectromagnetics* 26 (2005) 529–535.
- [53] H. Franke, J. Streckert, A. Bitz, J. Goeke, V. Hansen, E.B. Ringelstein, H. Nattkämper, H.J. Galla, F. Stögbauer, Effects of universal mobile telecommunications system (UMTS) electromagnetic fields on the BBB in vitro, *Radiat. Res.* 164 (2005) 258–269.
- [54] T. Sugimoto, G.J. Bennett, K.C. Kajander, Transsynaptic degeneration in the superficial dorsal horn after sciatic nerve injury: effects of a chronic constriction injury, transaction and strychnine, *Pain* 42 (1990) 205–213.
- [55] Z.S. Kherani, R.N. Auer, Pharmacologic analysis of the mechanism of dark neuron production in cerebral cortex, *Acta Neuropathol.* 116 (2008) 447–452.
- [56] D. Bexell, No neuronal apoptosis after EMF microwave exposure from mobile phones. Report supervised by Leif G. Salford at the Rausing Laboratory.
- [57] E. Kövesdi, J. Pál, F. Gallyas, The fate of “dark” neurons produced by transient focal cerebral ischemia in a non-necrotic and non-excitotoxic environment: neurobiological aspects, *Brain Res.* 1147 (2007) 272–283.
- [58] F. Gallyas, A. Csordás, A. Schwarcz, M. Mázló, “Dark” (compacted) neurons may not die through the necrotic pathway, *Exp. Brain Res.* 160 (2005) 473–486.
- [59] B. Söderfeldt, H. Kalimo, Y. Olsson, B.K. Siesjö, Bicucullineinduced epileptic brain injury. Transient and persistent cell changes in rat cerebral cortex in the early recovery period, *Acta Neuropathol.* 62 (1983) 87–95.
- [60] A. İlhan, A. Gurel, F. Armutcu, S. Kamisli, M. Iraz, O. Akyol, S. Ozen, *Ginkgo biloba* prevents mobile phone-induced oxidative stress in rat brain, *Clin. Chim. Acta* 340 (2004) 153–162.
- [61] F. Poulletier de Gannes, E. Haro, M. Taxile, E. Ladevze, L. Mayer, M. Lascau, P. Levêque, G. Ruffie, B. Billaudel, I. Lagroye, B. Veyret, Do GSM-900 signals affect blood–brain barrier permeability and neuron viability? in: Abstract at the 28th Annual Meeting of the Bioelectromagnetics Society, Cancun, Mexico, 2006, pp. 164–165.
- [62] K. Fredriksson, H. Kalimo, C. Norberg, B.B. Johansson, Y. Olsson, Nerve cell injury in the brain of stroke-prone spontaneously hypertensive rats *Acta Neuropathol. (Berl)* 76 (1988) 227–237.
- [63] T.S. Salahuddin, H. Kalimo, B.B. Johansson, Y. Olsson, Observations on exudation of fibronectin, fibrinogen and albumin in the brain after carotid infusion of hyperosmolar solutions. An immunohistochemical study in the rat indicating longlasting changes in the brain microenvironment and multifocal nerve cell injuries, *Acta Neuropathol. (Berl)* 76 (1988) 1–10.
- [64] S. Eimerl, M. Scramm, Acute glutamate toxicity in cultured cerebellar granule cells: agonist potency, effects of pH, Zn<sup>2+</sup> and the potentiation by serum albumin, *Brain Res.* 560 (1991) 282–290.
- [65] B. Hassel, E.G. Iversen, F. Fonnum, Neurotoxicity of albumin in vivo, *Neurosci. Lett.* 167 (1994) 29–32.
- [66] W.D. Dietrich, O. Alonsi, M. Halley, R. Busto, M.Y.-T. Globus, Intraventricular infusion of N-methyl-D-aspartate: 1. Acute blood–brain barrier consequences, *Acta Neuropathol.* 84 (1992) 621–629.
- [67] M.L. Crawford, Generation of Standard EM using TEM transmission cells, *IEEE Trans. Electromagn. Comput.* 16 (1974) 189–195.
- [68] L. Malmgren, Radio frequency systems for NMR imaging: coil development and studies of non-thermal biological effects. PhD Thesis. Lund, Sweden. Department of Applied Electronics, Lund University, 1998.
- [69] Y.-C. Kuo, C.-Y. Kuo, Electromagnetic interference in the permeability of saquinavir across the blood–brain barrier using nanoparticulate carriers, *Int. J. Pharm.* 351 (2008) 271–281.

Mechanisms of Harm; DNA Damage; Microwave RF Interacts  
with Molecular Structures; Dr. Paul Dart MD.; 2013



# Microwave RF Interacts with Molecular Structures



(Original art by Raychel Ciemma, Springfield, Oregon, for Paul Lee DO FAAO's book [Interface](#), used with permission.)

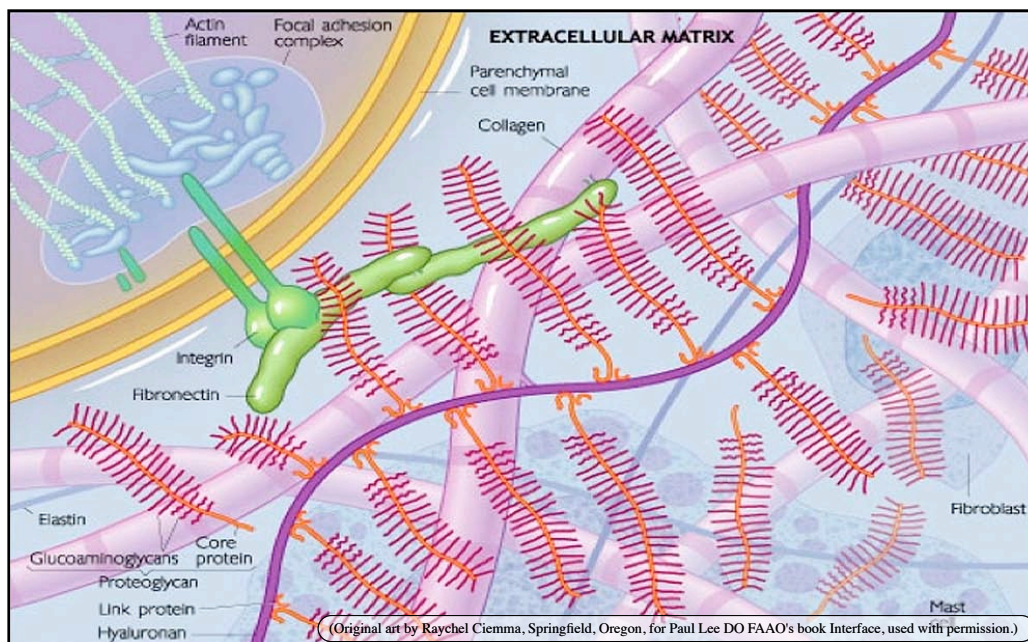
The molecules in our bodies vary in size and in total electric charge.

These molecular structures of our body can resonate with fluctuating electromagnetic fields.

Any charged particle has a resonant frequency.

This frequency varies depending on the total mass and charge of the particle.

## Molecules resonate in fluctuating electromagnetic fields.



(Original art by Raychel Ciemma, Springfield, Oregon, for Paul Lee DO FAAO's book [Interface](#), used with permission.)

The molecules in our bodies vary in size and total electric charge.

These molecular structures of our body resonate with fluctuating electromagnetic fields.

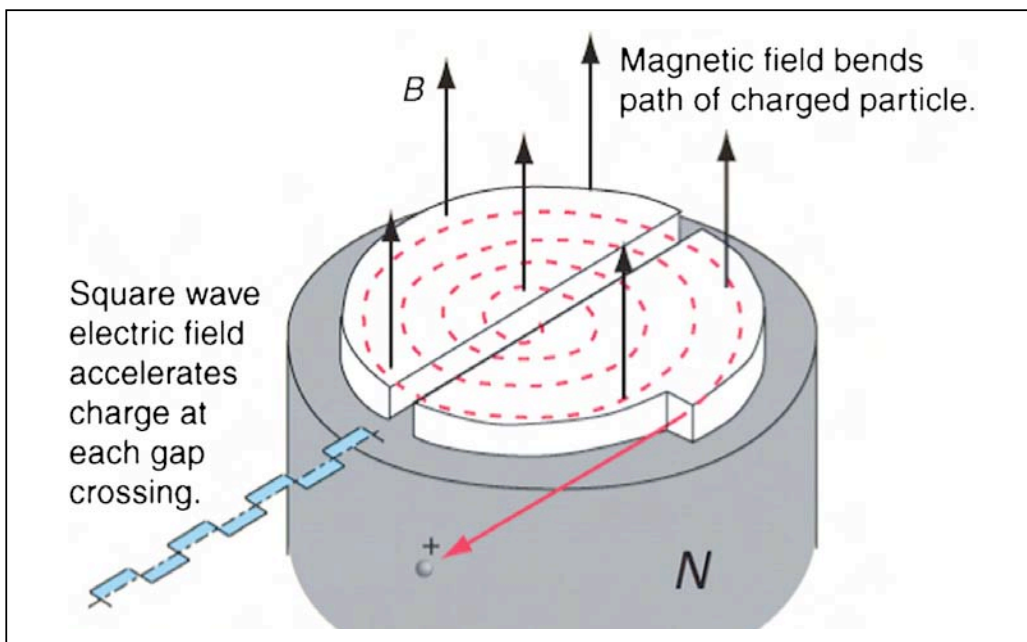


## Resonance Frequency



When you push something at its resonant frequency, a small force can produce a lot of motion.

## Resonance Frequency

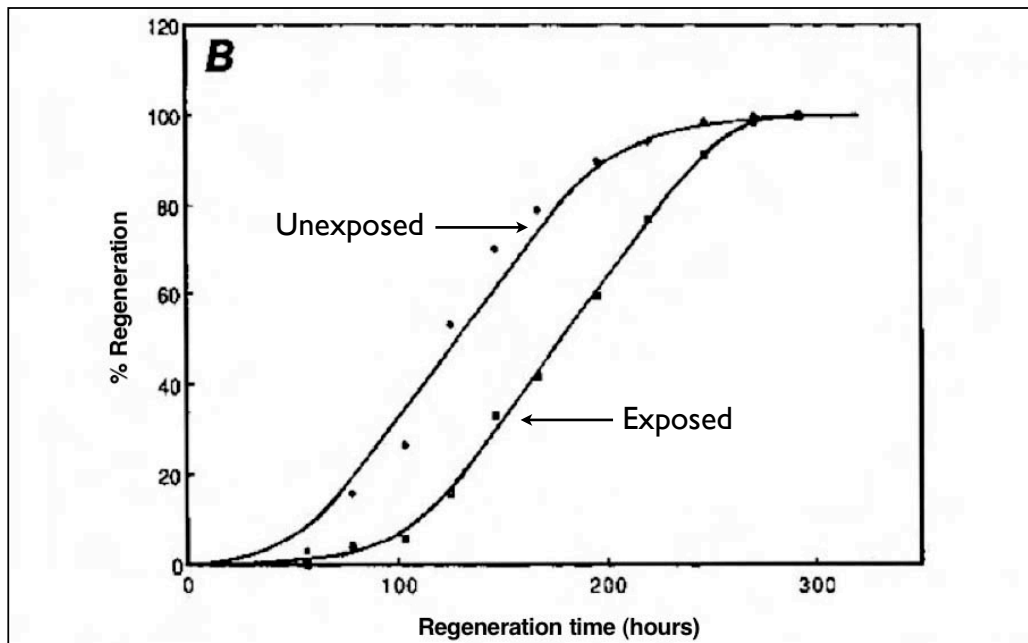


Placing the particle in an electromagnetic field that fluctuates at the resonant frequency will amplify the motion of the particle.

This is how a cyclotron works, and the frequency is often referred to as the "Ion Cyclotron Resonance" or ICR frequency.

Magnetic fields that fluctuate at the resonant frequency of an ion like calcium, or of a specific enzyme, can have dramatic effects on biochemical processes in the body.

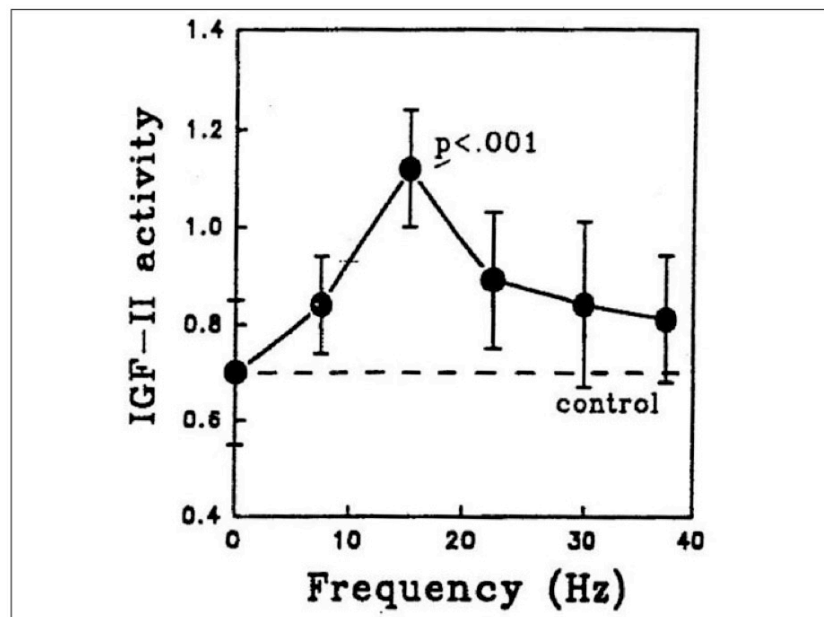
## Resonance Effect



Planaria exposed to a magnetic field fluctuating at the calcium ion's ICR frequency take far longer (48 hours) to regenerate than those that are not exposed.

Liboff A. Weak low-frequency electromagnetic fields are biologically interactive. In: Giuliani L, Soffritti M, eds. Non-Thermal Effects and Mechanisms of Interaction Between Electromagnetic Fields and Living Matter -- An ICEMS Monograph. Fidenza, Italy: Mattioli, (2010): 51-61. <http://www.ramazzini.it/ricerca/publications.asp>

## "frequency window"

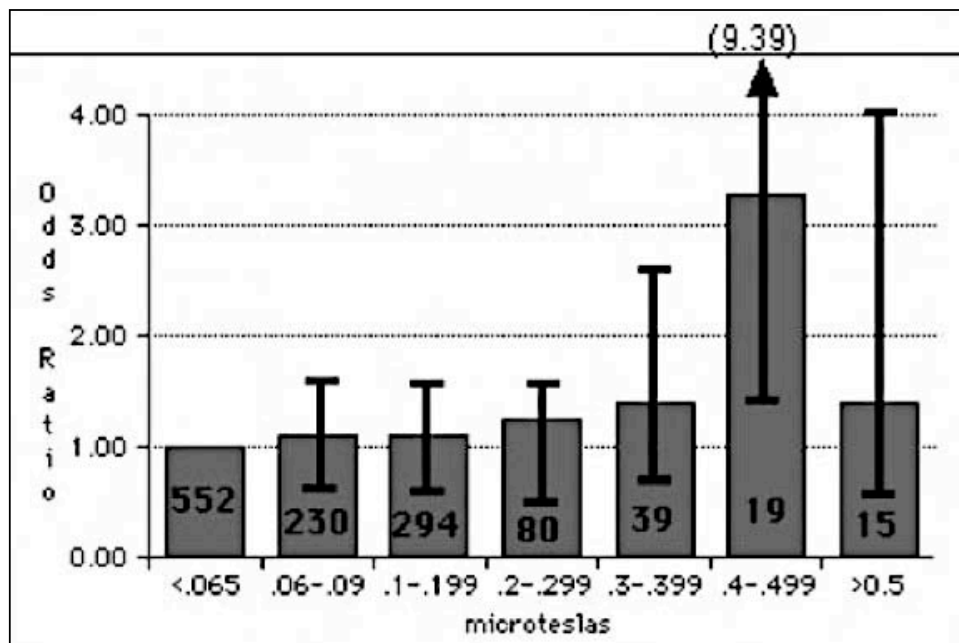


Some effects of fluctuating EMF occur at specific frequencies, called "frequency windows".

The peak in IGF-II expression for human osteosarcoma bone cells exposed to combined magnetic fields occurs when the field is tuned to the calcium ion's ICR frequency

Liboff A. Weak low-frequency electromagnetic fields are biologically interactive. In: Giuliani L, Soffritti M, eds. Non-Thermal Effects and Mechanisms of Interaction Between Electromagnetic Fields and Living Matter -- An ICEMS Monograph. Fidenza, Italy: Mattioli, (2010): 51-61. <http://www.ramazzini.it/ricerca/publications.asp>

### “power window”



At a given frequency, some power levels may have a different effect than others. This is a “power window”

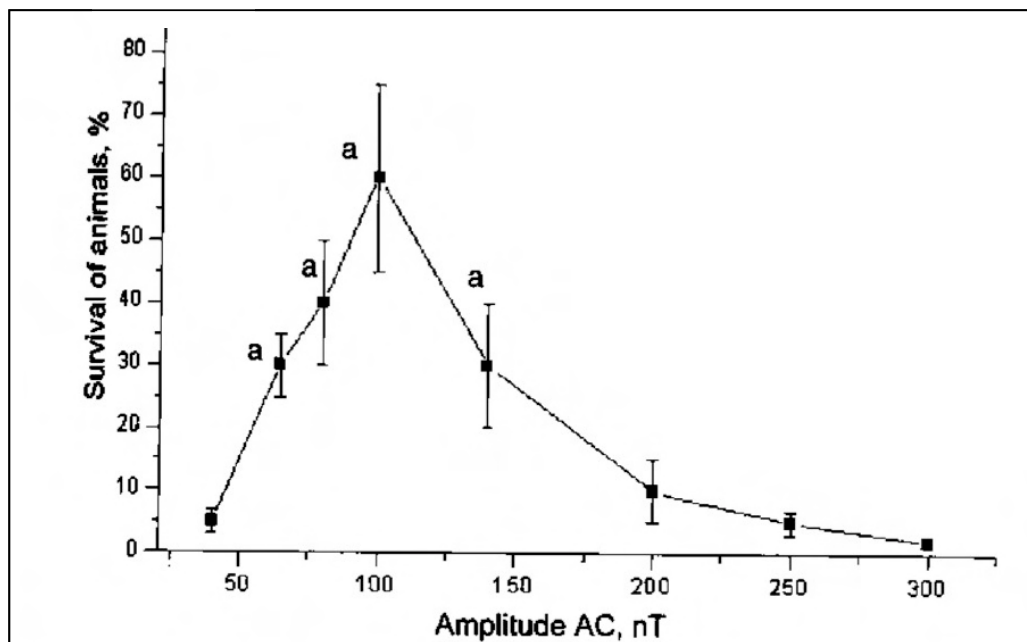
In this illustration, the odds ratio for childhood onset of Acute Lymphoblastic Leukemia is significantly higher if they are exposed to 60 cycle magnetic fields at a magnitude of 0.4 to 0.499 microtesla.

Lower and higher field magnitudes do not show the same effect.

Liboff A. Weak low-frequency electromagnetic fields are biologically interactive. In: Giuliani L, Soffritti M, eds. Non-Thermal Effects and Mechanisms of Interaction Between Electromagnetic Fields and Living Matter -- An ICEMS Monograph. Fidenza, Italy: Mattioli, (2010): 51-61. <http://www.ramazzini.it/ricerca/publications.asp>

Fig. 1. Odds ratios for childhood ALL, determined by Linet et al 6, as a function of residential magnetic field. The large ratios seen for fields between .4 and .499  $\mu$ T, although having many less participants, are nevertheless statistically significant

### “power window”



Mice with Ascites Ehrlich carcinoma 33,  
exposed to a fluctuating EM field tuned to the ICR frequency for aspartic acid and glutamic acid ions.  
Survival varies with the AMPLITUDE (magnitude) of the field.

Liboff A. Weak low-frequency electromagnetic fields are biologically interactive. In: Giuliani L, Soffritti M, eds. Non-Thermal Effects and Mechanisms of Interaction Between Electromagnetic Fields and Living Matter -- An ICEMS Monograph. Fidenza, Italy: Mattioli, (2010): 51-61. <http://www.ramazzini.it/ricerca/publications.asp>

Fig. 5. Survival curve for mice infected with Ascites Ehrlich carcinoma33, under ICR conditions corresponding to mean tuning (4.4 Hz) for aspartic acid and glutamic acid ions. In contrast to Fig. 2 where the frequency is varied, a resonance (or window) peak is observed as the AC magnetic field intensity is varied

What does this  
mean?



(Original art by Raychel Ciemma, Springfield, Oregon, for Paul Lee DO FAAO's book [Interface](#), used with permission.)

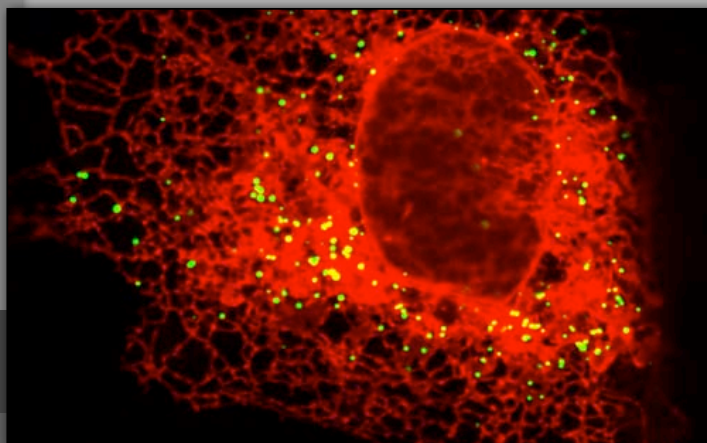
There are thousands of enzymes and other molecules in the human body.

Each has its own mass, charge, and resonant frequency.

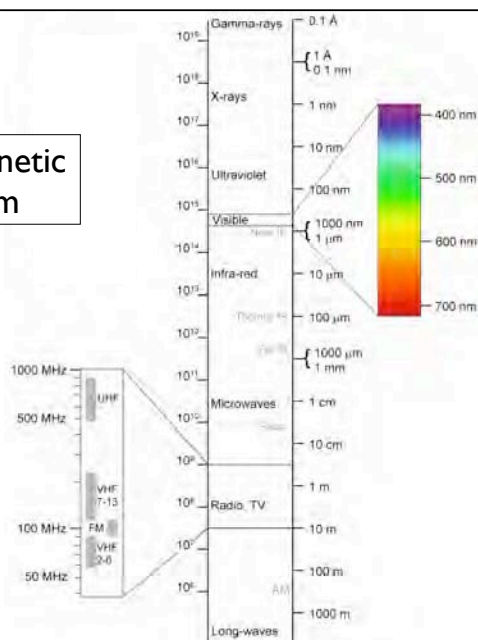
This means that different electromagnetic frequencies will resonate with different molecules.

Which means that the biological effects of EMF on molecular physiology are probably much more complex than is generally assumed to be the case.

# Microwave RF Produces Oxidative Stress in Cells



## Electromagnetic Spectrum



Ionizing radiation from the high energy end of the electromagnetic spectrum can directly break DNA molecular bonds, causing mutations.

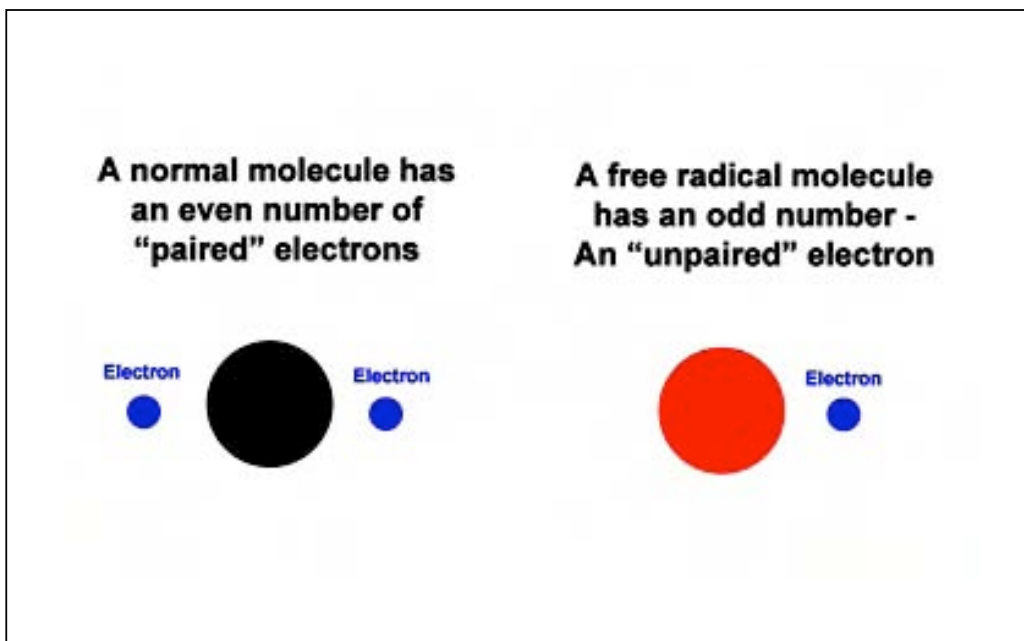
But photons of microwave RF do not have enough energy to directly break covalent molecular bonds.

Industry advocates often make the statement that since RF cannot break molecular bonds, there is no way that it can cause cancer.

Such statements sound like good physics. But they reflect a poor understanding of biology.

Tobacco can cause cancer. Genital warts can cause cancer. Asbestos can cause cancer. There are many ways to cause cancer besides ionizing radiation.

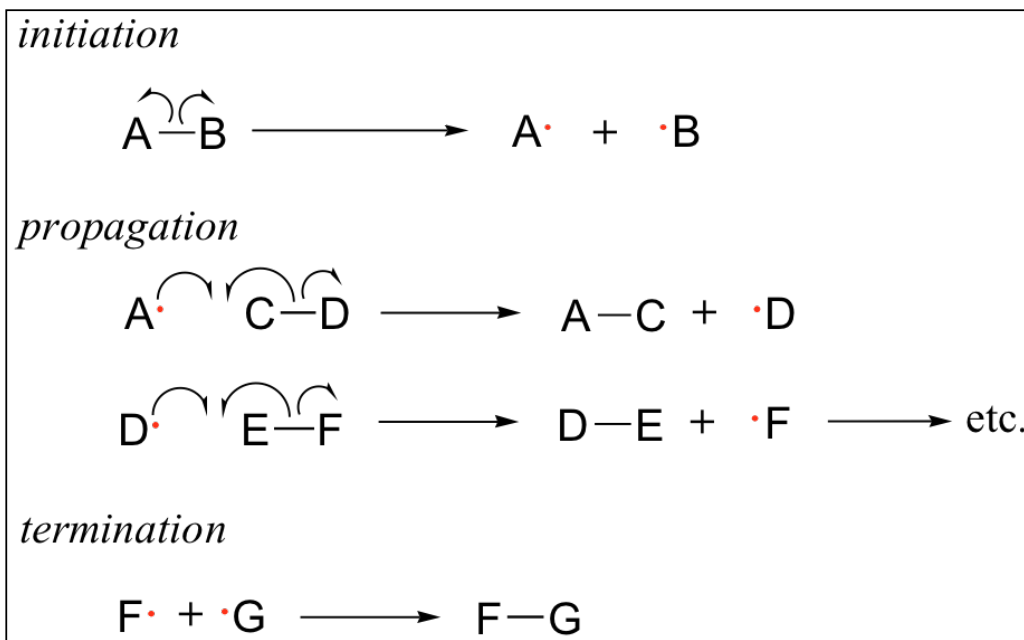
## Free Radicals



Free radicals are oxidizing agents.

They take electrons from other atoms or molecules, which can break molecular bonds.

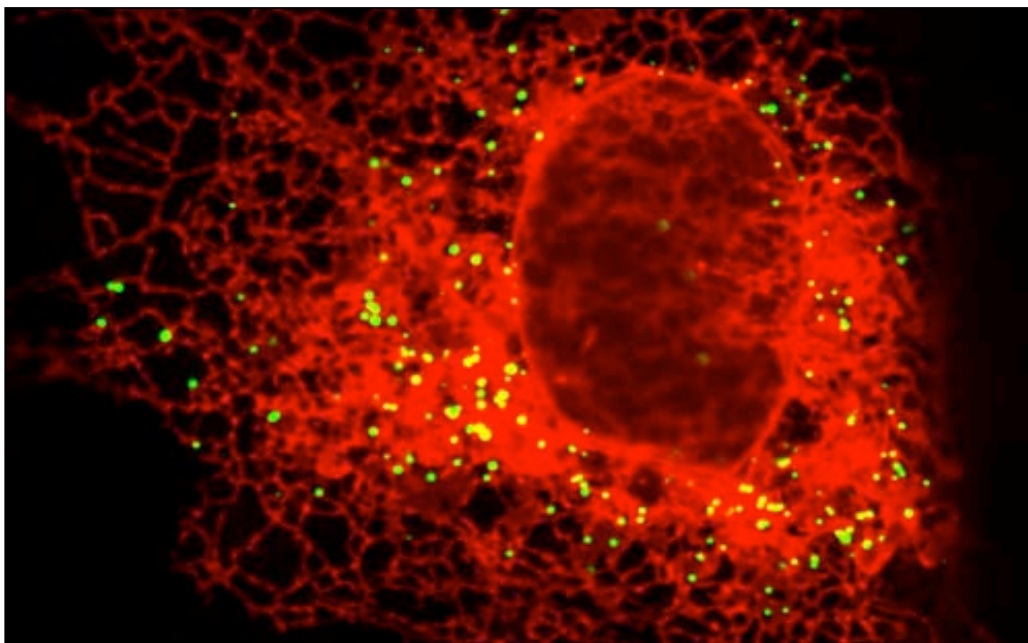
### Life cycle of a free radical.



Precursor molecule (AB) splits to form two free radicals.

Free radicals then can produce chain reactions, causing oxidative damage.





Peroxisomes (yellow) in a cell – packages of free radicals stored in cells.

Cells are making free radicals all the time.

Our bodies release them in inflammation to combat bacteria, remove diseased tissue, etc.

The free radicals release by the inflammatory process can break covalent bonds and fragment macromolecules.

<p><i>Review Article</i></p>	<p><i>J. Cell. Mol. Med. Vol XX, No X, 2013 pp. 1-9</i></p>
<p><b>Guest Editor:</b></p>	
<p><b>Electromagnetic fields act <i>via</i> activation of voltage-gated calcium channels to produce beneficial or adverse effects</b></p>	
<p><b>Martin L. Pall *</b></p>	
<p><i>Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, Portland, OR, USA</i></p>	
<p><i>Received: January 8, 2013; Accepted: May 20, 2013</i></p>	
<ul style="list-style-type: none"> <li>• Introduction</li> <li>• Possible modes of action following voltage-gated calcium channel stimulation</li> <li>• Therapeutic bone-growth stimulation <i>via</i> Ca<sup>2+</sup>/nitric oxide/cGMP/protein kinase G</li> </ul>	<ul style="list-style-type: none"> <li>• Ca<sup>2+</sup>/nitric oxide/peroxynitrite and pathophysiological responses to EMF exposures: the example of single-strand DNA breaks</li> <li>• Discussion and conclusions</li> </ul>
<p><b>Abstract</b></p> <p>The direct targets of extremely low and microwave frequency range electromagnetic fields (EMFs) in producing non-thermal effects have not been clearly established. However, studies in the literature, reviewed here, provide substantial support for such direct targets. Twenty-three studies have shown that voltage-gated calcium channels (VGCCs) produce these and other EMF effects, such that the L-type or other VGCC blockers block or greatly lower diverse EMF effects. Furthermore, the voltage-gated properties of these channels may provide biophysically</p>	

This recently published article reviews published evidence that EMF can produce physiologic effects by altering the function of voltage gated calcium channels in cell walls.

Pall ML. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med* (2013);

Table 1 EMF responses blocked or lowered by calcium channel blockers				
Ref. no.	EMF type	Calcium channel	Cell type or organism	Response measured
2	Pulsed magnetic fields	L-type	Human lymphocytes	Cell proliferation; cytokine production
3	Static magnetic field (0.1 T)	L-type	Human polymorphonuclear leucocytes	Cell migration; degranulation
5	ELF	L-type	Rat chromaffin cells	Differentiation; catecholamine release
6	Electric field	L-type	Rat and mouse bone cells	Increased $\text{Ca}^{2+}$ , phospholipase A2, PGE2
7	50 Hz	L-type	Mytilus (mussel) immunocytes	Reduced shape change, cytotoxicity
8	50 Hz	L-type	AtT20 D16V, mouse pituitary corticotrope-derived	$\text{Ca}^{2+}$ increase; cell morphology, premature differentiation
9	50 Hz	L-type	Neural stem/progenitor cells	<i>In vitro</i> differentiation, neurogenesis
10	Static magnetic field	L-type	Rat	Reduction in oedema formation
11	NMR	L-type	Tumour cells	Synergistic effect of EMF on anti-tumour drug toxicity
12	Static magnetic field	L-type	Myelomonocytic U937 cells	$\text{Ca}^{2+}$ influx into cells and anti-apoptotic effects
13	60 Hz	L-type	Mouse	Hyperalgesic response to exposure
14	Single nanosecond electric pulse	L-type	Bovine chromaffin cells	Very rapid increase in intracellular $\text{Ca}^{2+}$

These are some of the 23 published studies documenting that EMF can increase flow through these calcium channels, producing biological effects.

In all these studies, the effects of EMF on increased cellular calcium levels could be blocked by calcium channel blocking drugs.

Pall ML. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med* (2013);

15	Biphasic electric current	L-type	Human mesenchymal stromal cells	Osteoblast differentiation and cytokine production
16	DC & AC magnetic fields	L-type	$\beta$ -cells of pancreas, patch clamped	$\text{Ca}^{2+}$ flux into cells
17	50 Hz	L-type	Rat pituitary cells	$\text{Ca}^{2+}$ flux into cells
18	50 Hz	L-type, N-type	Human neuroblastoma IMR32 and rat pituitary GH3 cells	Anti-apoptotic activity
19	Nanosecond pulse	L-type, N-type, P/Q-type	Bovine chromaffin cells	$\text{Ca}^{2+}$ dynamics of cells
20	50 Hz	Not determined	Rat dorsal root ganglion cells	Firing frequency of cells
21	700–1100 MHz	N-type	Stem cell–derived neuronal cells	$\text{Ca}^{2+}$ dynamics of cells
22	Very weak electrical fields	T-type	Sharks	Detection of very weak magnetic fields in the ocean
23	Short electric pulses	L-type	Human eye	Effect on electro-oculogram
24	Weak static magnetic field	L-type	Rabbit	Baroreflex sensitivity
25	Weak electric fields	T-type	Neutrophils	Electrical and ion dynamics
26	Static electric fields, 'capacitive'	L-type	Bovine articular chondrocytes	Agrican & type II collagen expression; calcineurin and other $\text{Ca}^{2+}$ /calmodulin responses

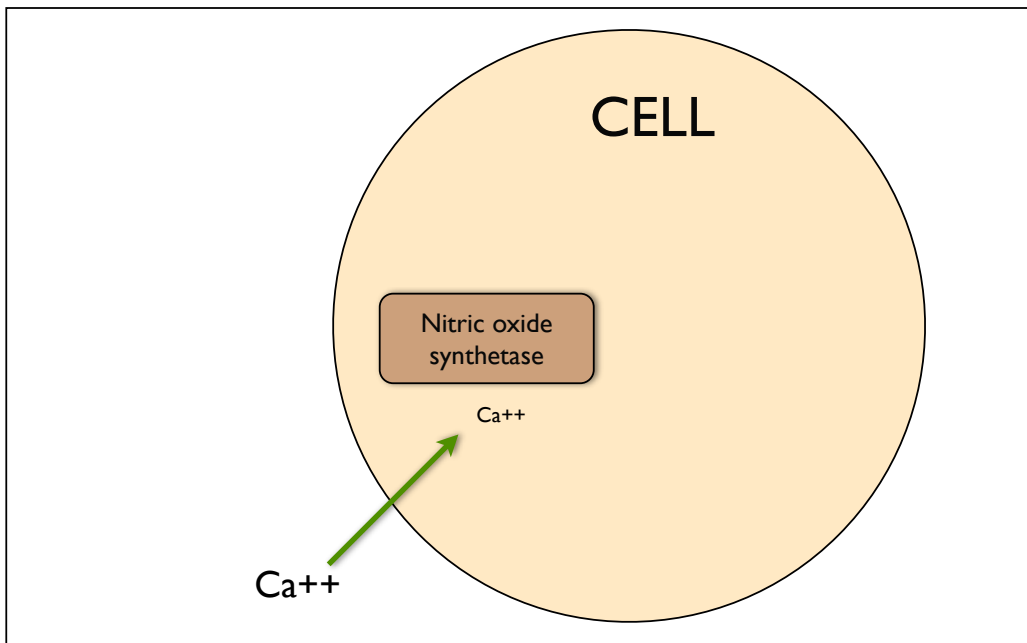
EMF: electromagnetic field; ELF: extremely low frequency.

In all these studies, the effects of EMF on increased cellular calcium levels could be blocked by calcium channel blocking drugs.

Pall ML. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med* (2013);



## EMF Activation of VGCCs Increases Free Radical Production



Normally, Calcium concentrations are much higher outside of cells than inside them.

Influxes of calcium into cells act as chemical signals to alter cellular physiologic activity.

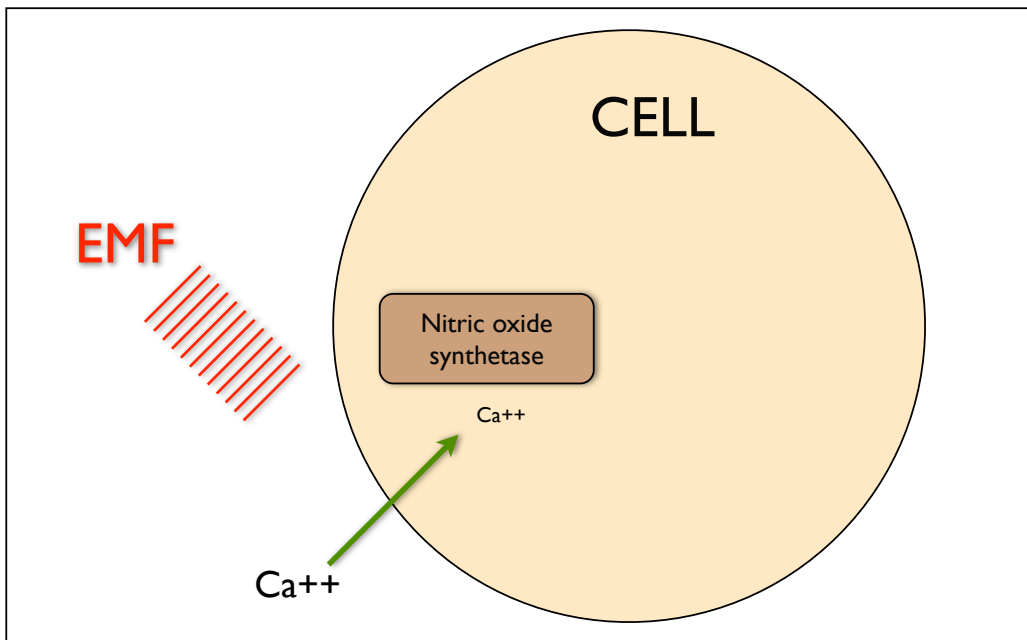
Here we have a diagram of a cell, with high levels of calcium outside, and lower levels of calcium inside.

The green arrow is a voltage-gated calcium channel, that can open to allow more calcium to enter the cell.

Inside the cell, we can see an enzyme (nitric oxide synthetase).

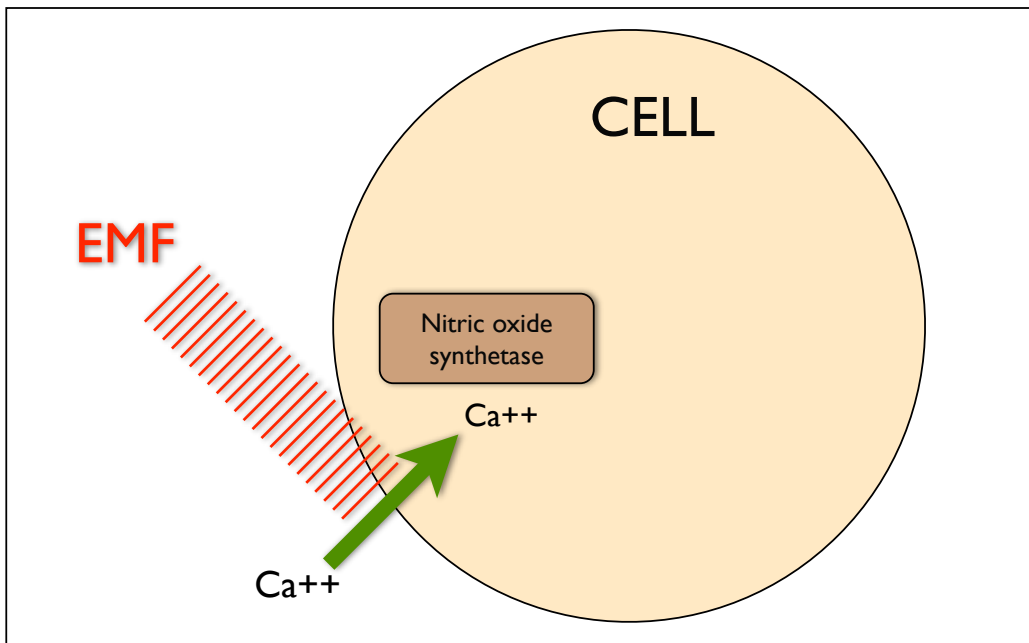
As discussed by Pall ML. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med* (2013);

## EMF Activation of VGCCs Increases Free Radical Production



An electromagnetic field arrives at the cell wall.

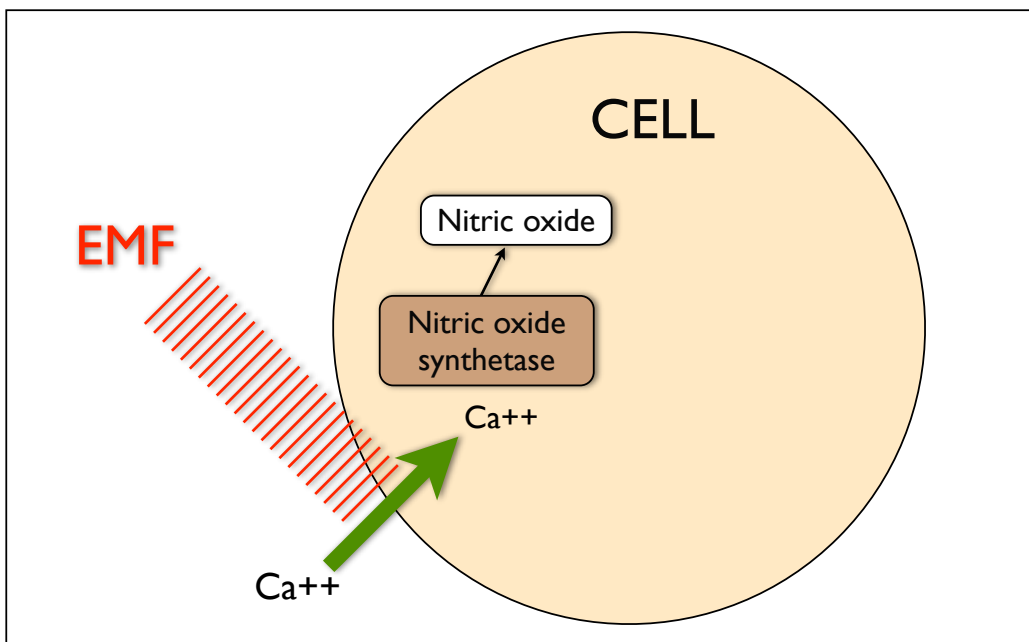
## EMF Activation of VGCCs Increases Free Radical Production



The electromagnetic field stimulates opening of voltage-gated calcium channels (VGCCs) in the cell membrane.

This increases  $\text{Ca}^{++}$  entry into the cell.

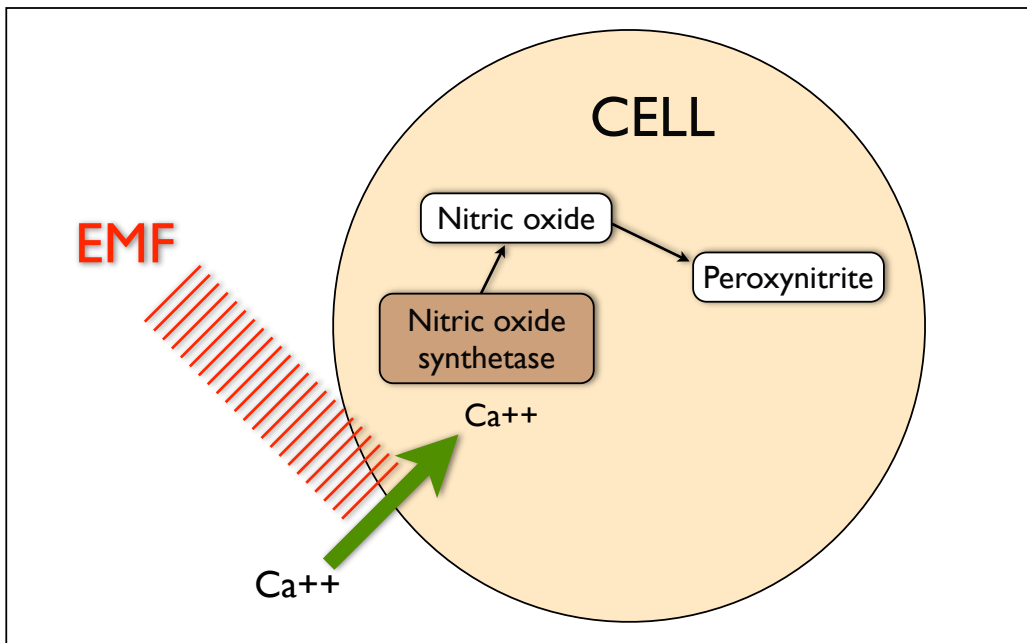
## EMF Activation of VGCCs Increases Free Radical Production



Increased intracellular calcium levels stimulate the activity of nitric oxide synthetase,

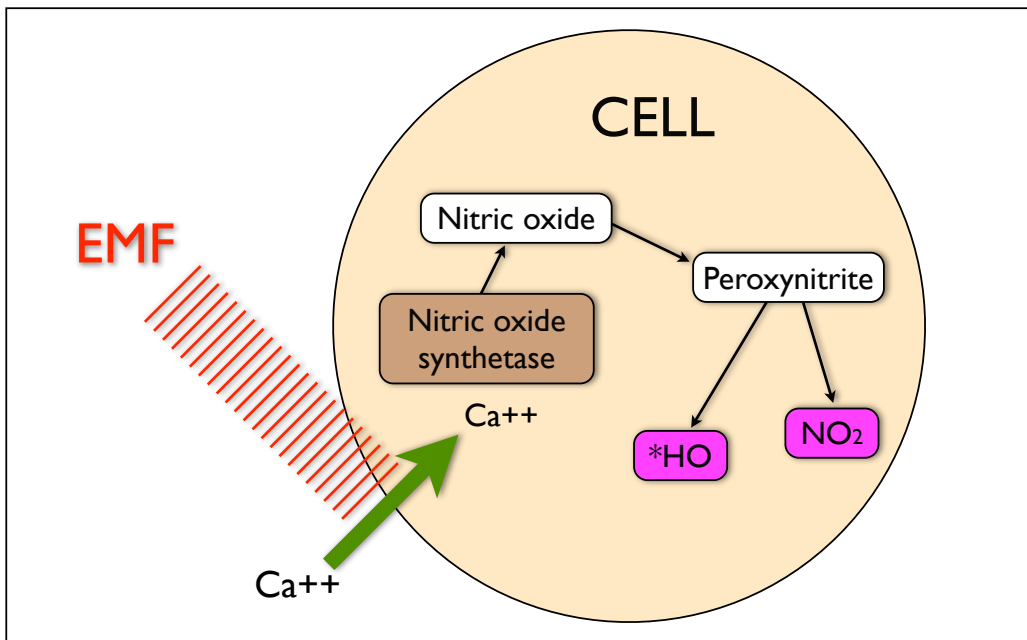
Which leads to increased production of nitric oxide in the cell.

## EMF Activation of VGCCs Increases Free Radical Production



Increased nitric oxide leads to increase in peroxynitrite, a potent non-radical oxidant.

## EMF Activation of VGCCs Increases Free Radical Production



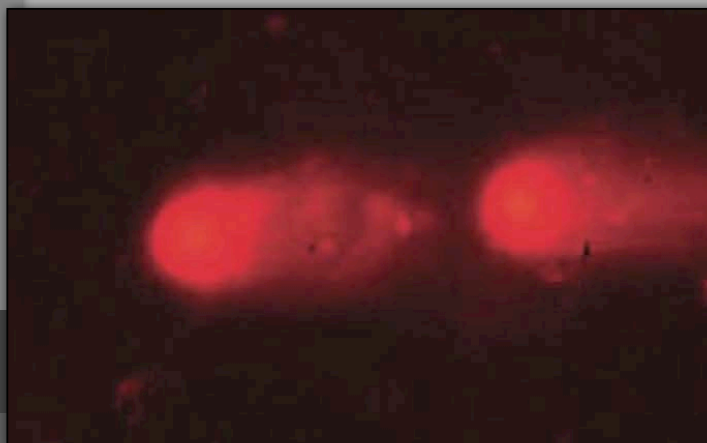
Peroxynitrite produces free radicals, including hydroxyl radical and  $\text{NO}_2$ .

This increase in free radicals then leads to inflammation, oxidant stress, and damage to cell structures, including DNA.

The EMF doesn't directly damage the cell. It just deranges cellular metabolism.

The free radicals that are produced by this change in metabolism are what causes the damage.

## Oxidative Stress From Microwave RF Damages DNA

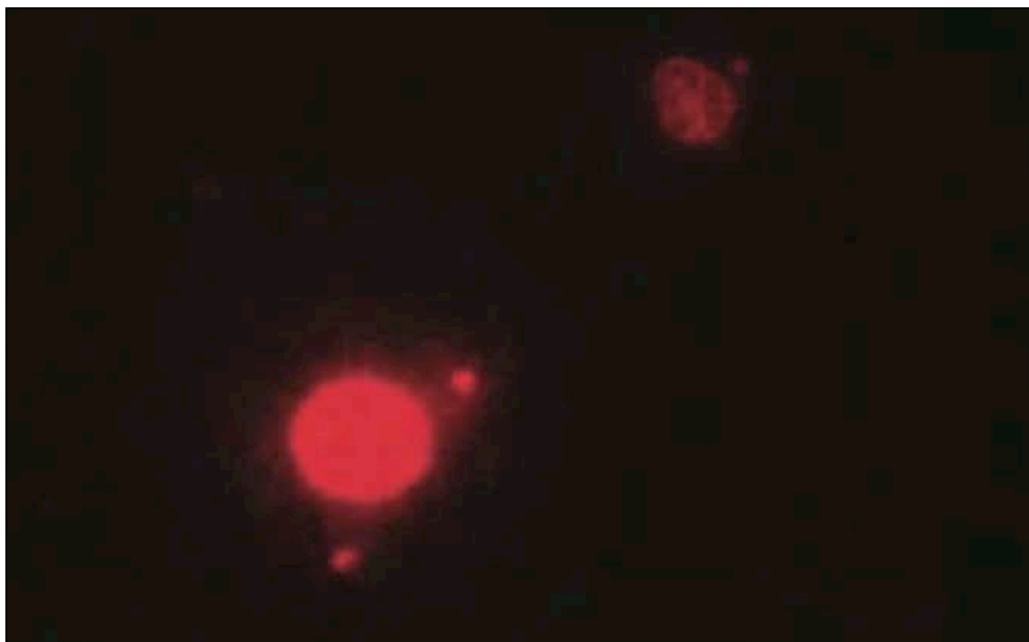


The mechanisms of **how** RF increases free radical activity and oxidative stress are still being explored.

But the fact that RF **does do this** has been CLEARLY ESTABLISHED by many research studies.

This increase in free radical levels can and does lead to DNA damage.

### Comet assay: Unexposed control



The Comet assay is one way to measure DNA damage.

This is a study of DNA extracted from normal rat brain cells (unexposed controls).

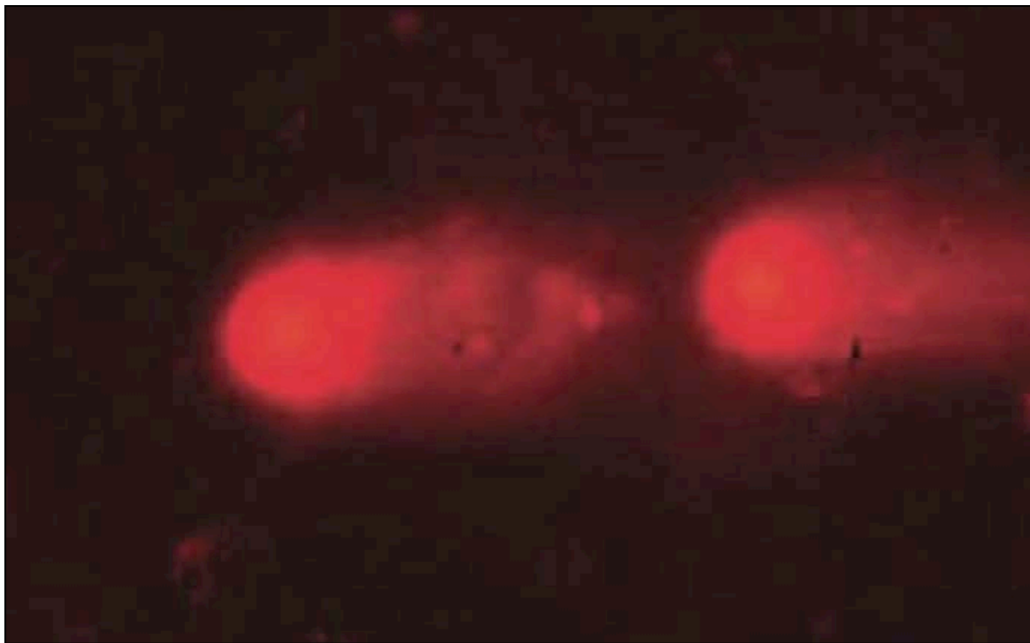
Electrophoresis: DNA molecules of given mass and charge placed in a diffusion medium.

Preparation placed in a static electric field.

DNA molecules migrate towards a charged pole.

DNA molecules that are the same size, so they migrate at the same rate, will stay in a clump.

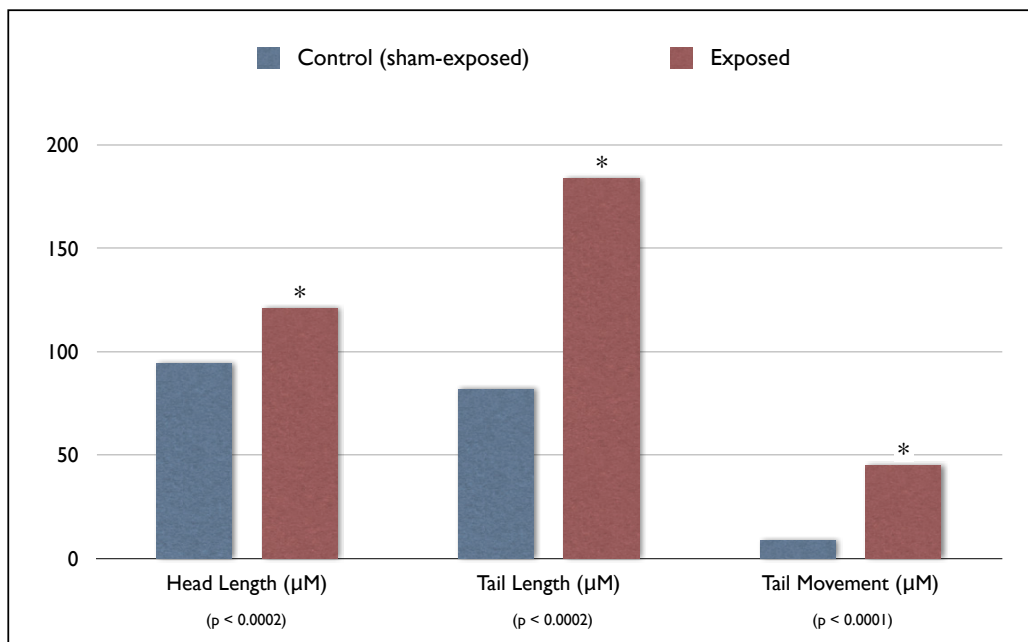
RF exposure: 2.45 GHz @ 0.34 mW/cm<sup>2</sup>, 2 hours per day x 35 days



DNA from brain cells of exposed rats. Here, some of the DNA molecules are broken. The broken parts vary in mass and total charge, so they migrate through the gel at different rates. This leaves a “comet tail” of lighter fragments behind the main body of intact DNA. The length of the tail can be measured. This is a **very sensitive** assay for DNA damage.

Kesari KK, Behari J, Kumar S. Mutagenic response of 2.45 GHz radiation exposure on rat brain. *Int J Radiat Biol* (2010a); 86(4):334-343.

RF exposure: 2.45 GHz @ 0.34 mW/cm<sup>2</sup>, 2 hours per day x 35 days



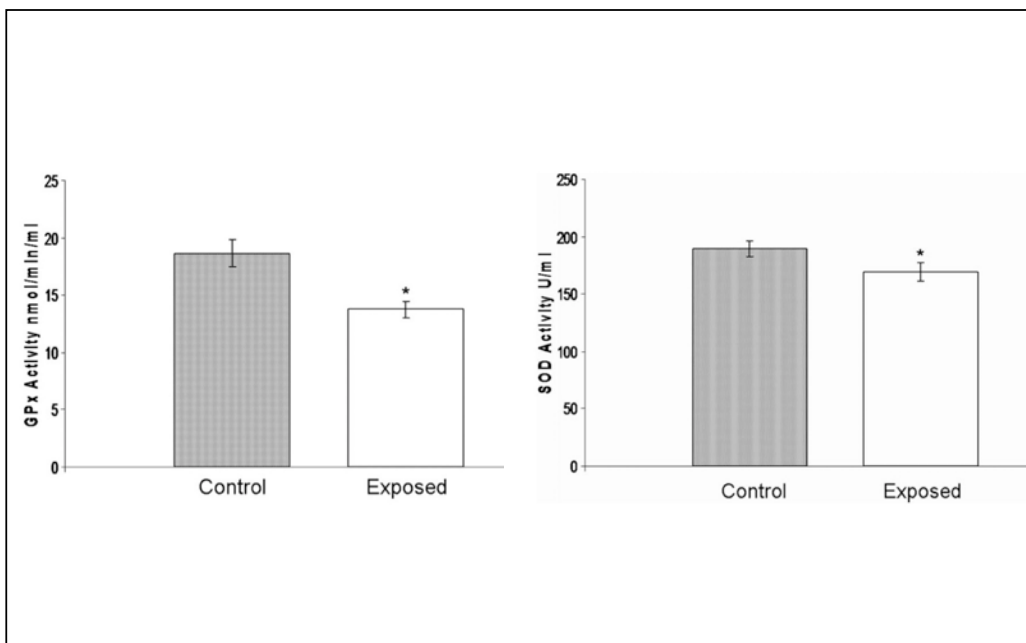
Comet Assay: **Measure of DNA fragmentation** in rat brains, produced by prolonged exposure to microwave RF.

In this study, exposure was 2 h a day for 35 days an exposure level of one third of the FCC exposure limit.

FCC exposure limit = 1 mW/cm<sup>2</sup>

Kesari KK, Behari J, Kumar S. Mutagenic response of 2.45 GHz radiation exposure on rat brain. *Int J Radiat Biol* (2010a); 86(4):334-343.

RF exposure: 2.45 GHz @ 0.34 mW/cm<sup>2</sup>, 2 hours per day x 35 days



#### Depletion of antioxidants in RF-exposed rat brains.

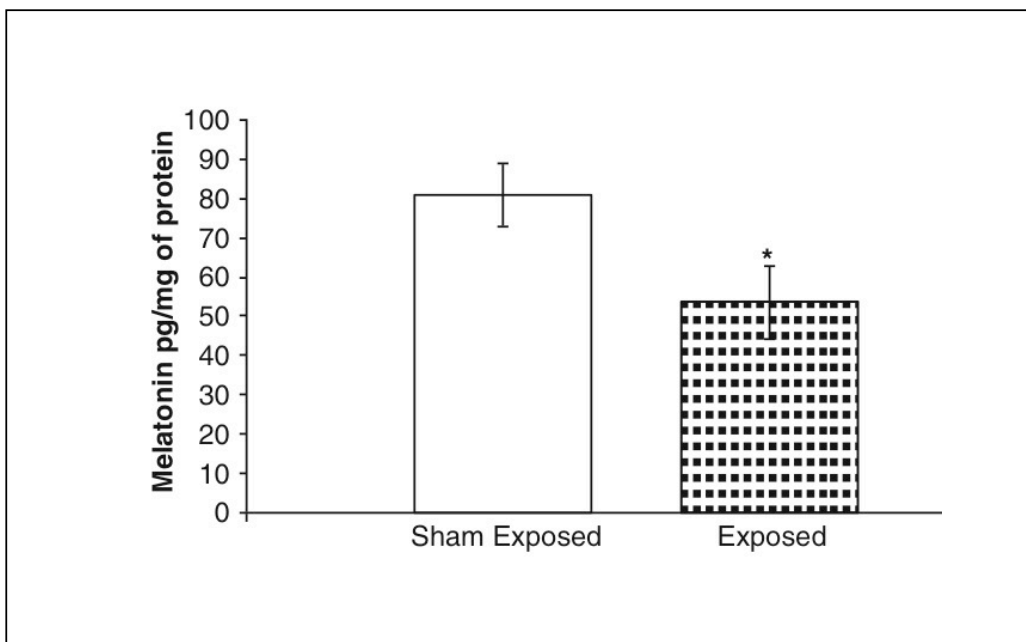
This consumption of anti-oxidants is **evidence of increased oxidant stress**, due to excess free radical production.

Kesari KK, Behari J, Kumar S. Mutagenic response of 2.45 GHz radiation exposure on rat brain. *Int J Radiat Biol* (2010a); 86(4):334-343.

#### Abstract

**Purpose:** To investigate the effect of 2.45 GHz microwave radiation on rat brain of male wistar strain. **Material and methods:** Male rats of wistar strain (35 days old with 130 ± 10 g body weight) were selected for this study. Animals were divided into two groups: Sham exposed and experimental. Animals were exposed for 2 h a day for 35 days to 2.45 GHz frequency at 0.34 mW/cm<sup>2</sup> power density. The whole body specific absorption rate (SAR) was estimated to be 0.11 W/Kg. Exposure took place in a ventilated Plexiglas cage and kept in anechoic chamber in a far field configuration from the horn antenna. After the completion of exposure period, rats were sacrificed and the whole brain tissue was dissected and used for study of double strand DNA (Deoxyribonucleic acid) breaks by micro gel electrophoresis and the statistical analysis was carried out using comet assay (IV-2 version software). Thereafter, antioxidant enzymes and histone kinase estimation was also performed. **Results:** A significant increase was observed in comet head (P50.002), tail length (P50.0002) and in tail movement (P 5 0.0001) in exposed brain cells. An analysis of antioxidant enzymes glutathione peroxidase (P 5 0.005), and superoxide dismutase (P50.006) showed a decrease while an increase in catalase (P50.006) was observed. A significant decrease (P 5 0.023) in histone kinase was also recorded in the exposed group as compared to the control (sham-exposed) ones. One-way analysis of variance (ANOVA) method was adopted for statistical analysis. **Conclusion:** The study concludes that the chronic exposure to these radiations may cause significant damage to brain, which may be an indication of possible tumour promotion (Behari and Paulraj 2007).

RF exposure: 2.45 GHz @ 0.21 mW/cm<sup>2</sup>, 2 hours per day x 45 days



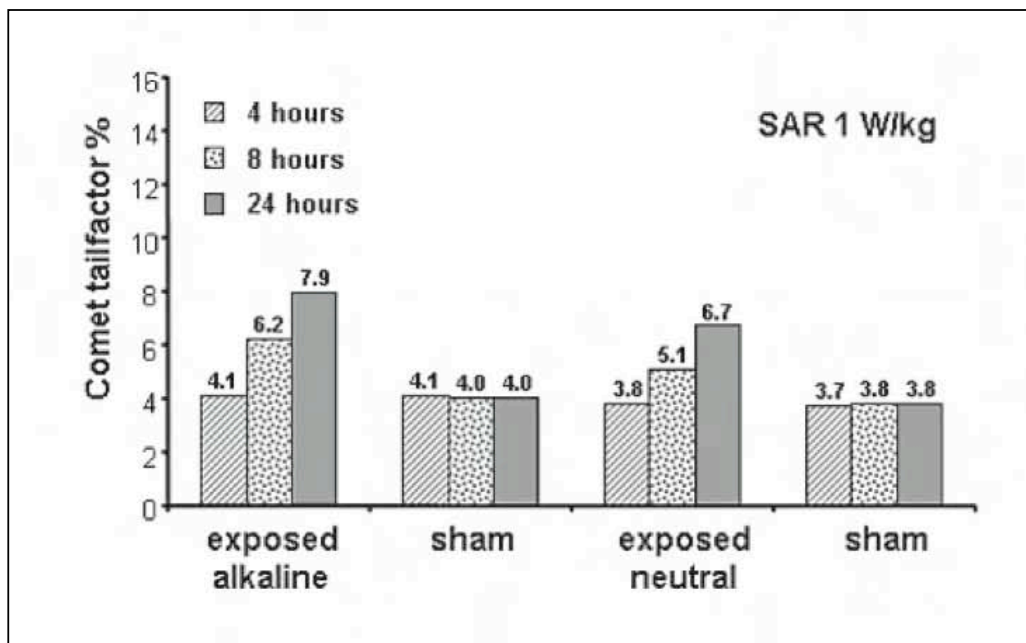
#### Suppression of melatonin secretion by 2.45 GHz RF:

Bad news, since melatonin is also a potent antioxidant.

Kesari KK, Kumar S, Behari J. Pathophysiology of microwave radiation: effect on rat brain. *Appl Biochem Biotechnol* (2012); 166(2):379-388.

10 MINUTE BREAK HERE

## Evidence of DNA damage by microwave RF.

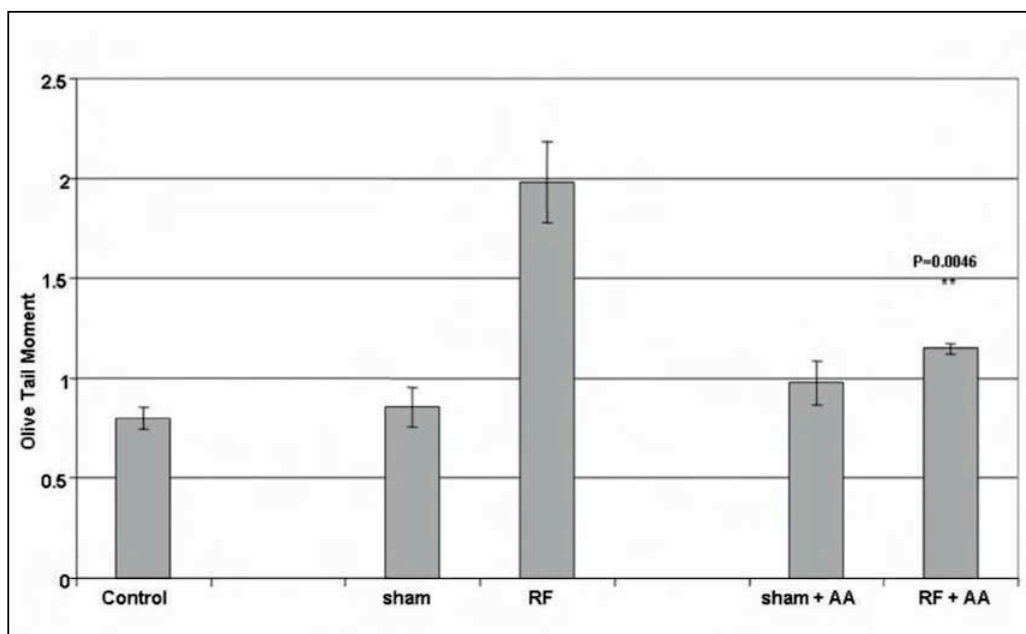


Another study, using Human fibroblasts.  
1950 MHz, 5 minutes on/10 minutes off.  
Total exposure for 4, 8, or 24 hours.  
DNA fragmentation measured by Comet Assay.

**Figure 9.** Intermittent RF-EMF exposure (1950 MHz, 5 minutes on/10 minutes off, 1 and 2 W/kg, 4, 8 and 24 hours) increases the DNA strand break frequency in human fibroblasts dependent on the duration of exposure as measured with the alkaline and neutral Comet assay (H.-W. Rüdiger et al., Division of Occupational Medicine, University of Vienna, Austria).

Adlkofer F. Risk Evaluation of Potential Environmental Hazards from Low Energy Electromagnetic Field Exposure Using Sensitive In Vitro Methods. *Bioelectromagnetics* (2006); 331-354.

## DNA damage blocked by anti-oxidants



A cell study, with human fibroblasts, exposed to 1950 MHz RF, 5 minutes on/10 minutes off.

(right hand columns => **DNA damage blocked by anti-oxidant effect of vitamin C (ascorbic acid).**

The research group of Prof. Tauber, Berlin, investigated the effect of RF-EMF on HL-60 cells, i.e. a human promyelocytic cell line. After continuous exposure to RF-EMF of 1800 MHz and a SAR value of 1.3 W/kg they observed a highly significant increase in the number of single and double DNA strand breaks as measured by the alkaline Comet assay and of micronuclei as measured with the micronucleus test, thus fully confirming the findings obtained in the Vienna laboratory. Additionally, as clearly shown in Figures 12 and 13, the generation of DNA strand breaks and micronuclei can be prevented, when the radical scavenger ascorbic acid is added to the culture medium before exposure.

Figure 12, from: Adlkofer F. Risk Evaluation of Potential Environmental Hazards from Low Energy Electromagnetic Field Exposure Using Sensitive In Vitro Methods. *Bioelectromagnetics* (2006); 331-354.

Medical Treatments & Modulation; Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. British Journal of Cancer. (Costa et al); 2011



# Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields

FP Costa<sup>\*,1</sup>, AC de Oliveira<sup>1</sup>, R Meirelles<sup>1</sup>, MCC Machado<sup>1</sup>, T Zanesco<sup>1</sup>, R Surjan<sup>1</sup>, MC Chammas<sup>2</sup>, M de Souza Rocha<sup>2</sup>, D Morgan<sup>3</sup>, A Cantor<sup>4</sup>, J Zimmerman<sup>5</sup>, I Brezovich<sup>6</sup>, N Kuster<sup>7</sup>, A Barbault<sup>8</sup> and B Pasche<sup>\*,5</sup>

<sup>1</sup>Department of Transplantation and Liver Surgery, Hospital das Clínicas da Faculdade de Medicina, University of São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 255, São Paulo 05403-000, Brazil; <sup>2</sup>Department of Radiology, Hospital das Clínicas, University of São Paulo, São Paulo 05403-000, Brazil;

<sup>3</sup>Department of Radiology, University of Alabama at Birmingham and UAB Comprehensive Cancer Center, Birmingham, AL 35294, USA; <sup>4</sup>Biostatistics and Bioinformatics Shared Facility, University of Alabama at Birmingham and UAB Comprehensive Cancer Center, Birmingham, AL 35294, USA; <sup>5</sup>Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham and UAB Comprehensive Cancer Center, 1802 6th Ave South, NP 2566, Birmingham, AL 35294-3300, USA; <sup>6</sup>Department of Radiation Oncology, The University of Alabama at Birmingham and UAB Comprehensive Cancer Center, Birmingham, AL 35294, USA; <sup>7</sup>IT'IS Foundation, Swiss Federal Institute of Technology, Zurich, Switzerland; <sup>8</sup>Rue de Verdun 20, Colmar 68000, France

**BACKGROUND:** Therapeutic options for patients with advanced hepatocellular carcinoma (HCC) are limited. There is emerging evidence that the growth of cancer cells may be altered by very low levels of electromagnetic fields modulated at specific frequencies.

**METHODS:** A single-group, open-label, phase I/II study was performed to assess the safety and effectiveness of the intrabuccal administration of very low levels of electromagnetic fields amplitude modulated at HCC-specific frequencies in 41 patients with advanced HCC and limited therapeutic options. Three-daily 60-min outpatient treatments were administered until disease progression or death. Imaging studies were performed every 8 weeks. The primary efficacy end point was progression-free survival  $\geq 6$  months. Secondary efficacy end points were progression-free survival and overall survival.

**RESULTS:** Treatment was well tolerated and there were no NCI grade 2, 3 or 4 toxicities. In all, 14 patients (34.1%) had stable disease for more than 6 months. Median progression-free survival was 4.4 months (95% CI 2.1–5.3) and median overall survival was 6.7 months (95% CI 3.0–10.2). There were three partial and one near complete responses.

**CONCLUSION:** Treatment with intrabuccally administered amplitude-modulated electromagnetic fields is safe, well tolerated, and shows evidence of antitumour effects in patients with advanced HCC.

*British Journal of Cancer* (2011) **105**, 640–648. doi:10.1038/bjc.2011.292 www.bjcancer.com

Published online 9 August 2011

© 2011 Cancer Research UK

**Keywords:** hepatocellular carcinoma; phase II study; radiofrequency electromagnetic fields; tumour-specific modulation frequencies; 27.12 MHz

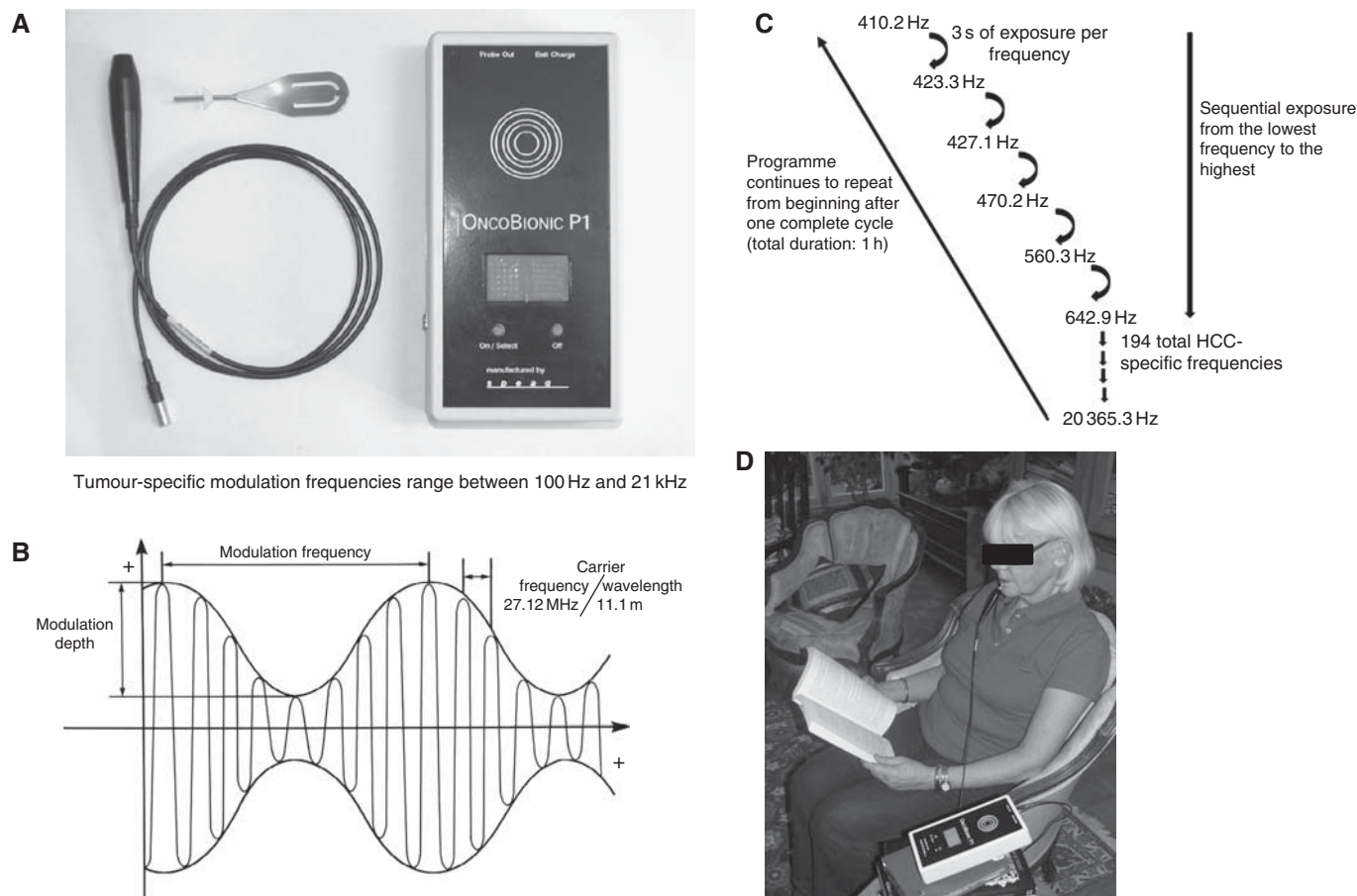
Treatment of inoperable or metastatic solid tumours is a major challenge in oncology, which is limited by the small number of therapeutic agents that are both well tolerated and capable of long-term control of tumour growth. Hepatocellular carcinoma (HCC) is the second most common cause of cancer death in men and the sixth in women worldwide (Jemal *et al*, 2011). Hepatocellular carcinoma is the most common tumour in certain parts of the world, particularly in East Asia, Africa, and certain countries of South America. This tumour is less frequent in Europe and in the United States, but has become the fastest rising cancer in the United States (Jemal *et al*, 2011). In the United States alone, it is estimated that 24 120 new cases were diagnosed and there were 17 430 deaths from HCC in 2010 (Jemal *et al*, 2010), a 27% increase in the number of new cases since 2004 (Jemal *et al*, 2004). The

prognosis of patients suffering from advanced HCC is poor with an average survival of fewer than 6 months (Kassianides and Kew, 1987; Jemal *et al*, 2011).

Therapies for HCC are limited. Resections of the primary tumour or liver transplantation are the preferred therapeutic approaches in patients who are surgical candidates (Bruix and Sherman, 2005). Although these interventions result in long-term survival for some patients, only a minority benefit from them because of limitations due to tumour size, patient's overall condition, and presence of hepatic cirrhosis (Cance *et al*, 2000). Only a small number of randomised trials show a survival benefit in the treatment of HCC. Chemoembolisation has been shown to confer a survival benefit in selected patients with unresectable HCC (Llovet *et al*, 2002). Data from two phase III randomised placebo-controlled studies demonstrate improved survival in patients with advanced HCC receiving the multikinase inhibitor sorafenib (Llovet *et al*, 2008b; Cheng *et al*, 2009). Additional therapies for this disease are sorely needed, especially for the large number of patients with advanced disease who cannot tolerate

\*Correspondence: Dr FP Costa; E-mail: fredericoperegocosta@gmail.com or Dr B Pasche; E-mail: Boris.Pasche@ccc.uab.edu

Revised 4 July 2011; accepted 6 July 2011; published online 9 August 2011



**Figure 1** Delivery of HCC-specific modulation frequencies. **(A)** The generator of AM EMFs is a battery-driven RF EMF generator connected to a spoon-shaped mouthpiece. **(B)** Schematic description of AM EMFs. The carrier frequency (27.12 MHz) is sinusoidally modulated at specific frequencies. **(C)** Patient receiving treatment with RF AM EMF. **(D)** HCC treatment programme consisting of sequential emission of 194 modulation frequencies for 60 min.

chemotherapy or intrahepatic interventions because of impaired liver function (Thomas and Zhu, 2005).

The intrabuccal administration of low and safe levels of electromagnetic fields, which are amplitude-modulated at disease-specific frequencies (RF AM EMF) (Figure 1), was originally developed for the treatment of insomnia (Pasche *et al*, 1990). The highest levels of EMFs encountered during treatment are found at the interface between the tongue and the mouth probe and are compliant with international safety limits (ICNIRP, 1998; Pasche and Barbault, 2003). Tumour-specific modulation frequencies have been identified for several common forms of cancer and one report suggests that this novel therapeutic approach is well tolerated and may be effective in patients with a diagnosis of cancer (Barbault *et al*, 2009). However, the safety and potential efficacy of this treatment approach in the treatment of advanced HCC are unknown. We designed this single-group, open-label, phase I/II study to assess the feasibility of this treatment in patients with advanced HCC and limited therapeutic options.

## PATIENTS AND METHODS

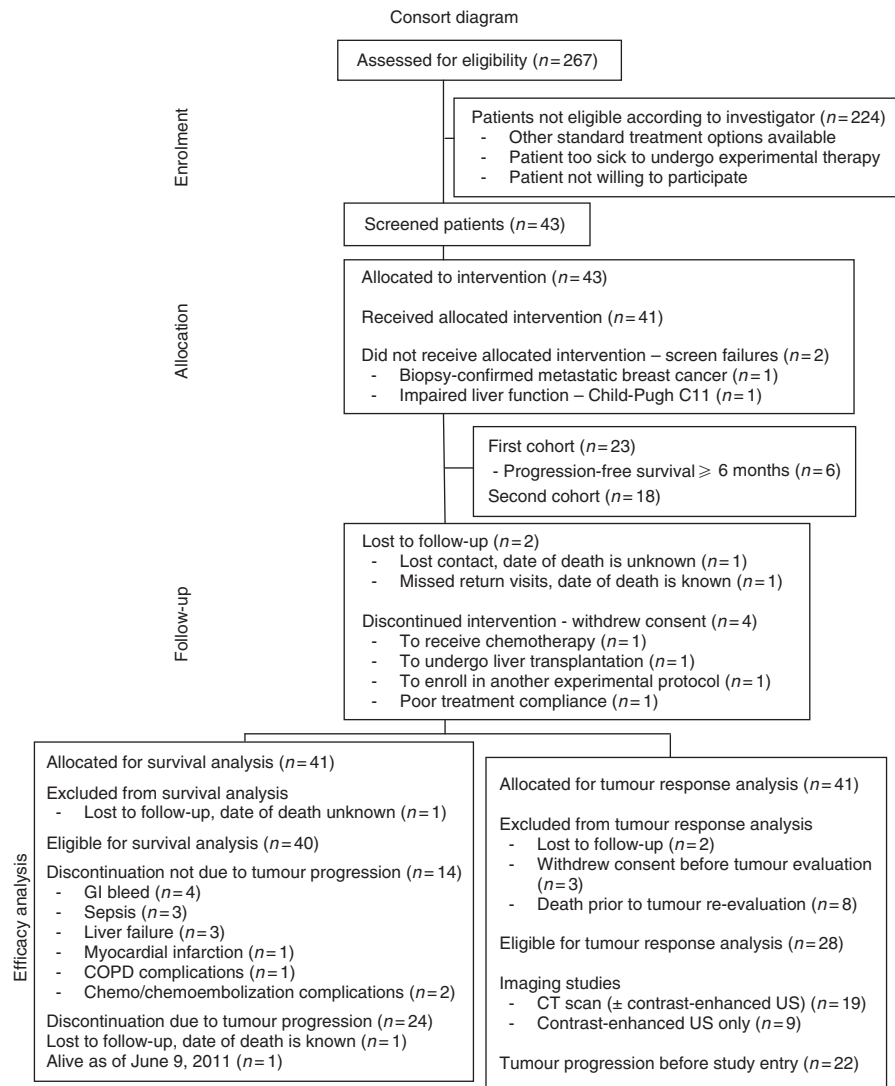
### Patients

The study was aimed at offering treatment to patients with Child–Pugh A or B advanced HCC and limited therapeutic options. Patients were classified as having advanced disease if they were not

eligible for surgical resection or had disease progression after surgical or locoregional therapies or had disease progression after chemotherapy or sorafenib therapy. Patients with measurable, inoperable HCC were eligible for enrolment. Previous local or systemic treatments were allowed as long as they were discontinued at least 4 weeks before enrolment. Inclusion criteria included Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and biopsy-confirmed HCC. Also allowed were patients with no pathological confirmation of HCC with a level of  $\alpha$ -fetoprotein higher than  $400 \text{ ng ml}^{-1}$  and characteristic imaging findings as assessed by multislice computer tomography (CT) scan or intravenous contrast ultrasound (US). As per the University of São Paulo Department of Transplantation and Liver Surgery guidelines, liver biopsies are avoided in patients eligible for transplant or with severely impaired liver function. Exclusion criteria included confirmed or suspected brain metastasis, Child–Pugh C, previous liver transplant, and pregnancy.

### Study design

This was an investigator-initiated, single centre, uncontrolled phase I/II trial in patients with advanced HCC. The trial was approved by the local human investigation committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. The protocol was registered: clinicaltrial.gov identifier no. NCT00534664.



**Figure 2** CONSORT diagram.

### Administration of AM EMFs

The generator of AM EMFs consists of a battery-driven radio-frequency (RF) EMF generator connected to a 1.5 m long 50 Ω coaxial cable, to the other end of which a stainless-steel spoon-shaped mouthpiece is connected via an impedance transformer (Figure 1A). The RF source of the device corresponds to a class C amplifier operating at 27.12 MHz. The carrier frequency is AM (Figure 1B) with a modulation depth of  $85 \pm 5\%$ , whereas the modulation frequency is generated by a digital direct synthesiser with a resolution of  $10^{-7}$ . The treatment sequence is controlled by a microcontroller (Atmel AT89S8252, Fribourg, Switzerland), that is, duration of session, sequence of modulation frequencies and duration of each sequence can be programmed via PC over a RS232 interface. The RF output is adjusted to 100 mW into a 50 Ω load, which results in an emitting power identical to that of the device used for the treatment of insomnia (Pasche *et al*, 1990; Reite *et al*, 1994; Pasche *et al*, 1996). The United States Food and Drug Administration has determined that such a device is not a significant risk device and it has been used in several studies conducted in the United States (Reite *et al*, 1994; Pasche *et al*, 1996; Kelly *et al*, 1997). A long-term follow-up survey of 807 patients who have received this therapy in the United States, Europe and

Asia showed that the rate of adverse reactions was low and was not associated with increases in the incidence of malignancy or coronary heart disease (Amato and Pasche, 1993). The maximum specific absorption rate (SAR) of the applied RF averaged over any 10 g of tissue has been estimated to be less than  $2 \text{ W kg}^{-1}$ , and the maximum temperature increase is significantly lower than  $1^\circ\text{C}$  anywhere in the body owing to RF absorption. The induced RF field values within the primary and metastatic tumours are significantly lower. In contrast, the RF fields induced during RF ablation of tumours cause hyperthermia and result in SAR in the range of  $2.4 \times 10^5 \text{ W kg}^{-1}$  (Chang, 2003), that is, more than 100 000 times higher than those delivered by the device used in this study.

We have previously reported the discovery of HCC-specific modulation frequencies in 46 patients with HCC using a patient-based biofeedback approach and shown the feasibility of using AM EMFs for the treatment of patients with cancer (Barbault *et al*, 2009). The treatment programme used in this study consisted of three-daily outpatient treatments of 1 h duration, which contained HCC-specific modulation frequencies ranging between 100 Hz and 21 kHz administered sequentially, each for 3 s (Figure 1C and Supplementary Table S1).

The treatment method consists of the administration of AM EMFs by means of an electrically conducting mouthpiece, which is

in direct contact with the oral mucosa (Figure 1D). The patients were instructed on the use of the device and received the first treatment at the medical centre's outpatient clinic. A device was provided to each patient for the duration of the study. The patients were advised to self-administer treatment three times a day. Treatment was administered until tumour progression was objectively documented. At that time, treatment was discontinued. Treatment compliance was assessed at every return visit by recording the number of treatments delivered in the preceding 2 months.

### Efficacy end points and disease assessment

The primary end point of this trial was the proportion of patients progression-free at 6 months. Secondary end points were progression-free survival (PFS) (first day of treatment until progression of disease or death) and overall survival (OS) (first day of receiving treatment to death). Objective response was assessed using the Response Evaluation Criteria in Solid Tumours group classification for patients with disease assessed by either helical multiphasic CT (Therasse *et al*, 2000). Whenever contrast-enhanced US radiological assessment was used, it was performed and reviewed by the same radiologist specialised in HCC (MCC) as this imaging modality is investigator dependent. Tumour measurements were performed at baseline and every 8 weeks. Only patients with at least one repeat tumour measurement during therapy were considered for response analysis. Throughout the study, lesions measured at baseline were evaluated using the same technique (CT or contrast-enhanced US). Overall tumour response was scored as a complete response (CR), partial response (PR), or stable disease (SD) if the response was confirmed at least 4 weeks later. Alpha-fetoprotein (AFP) levels were measured every 8 weeks in all patients throughout the study, but changes in AFP were not an end point for assessment of response. Pain was assessed according to the NCI-CTCAE v.3.0 ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf)).

### Statistical analyses and efficacy assessment

All eligible patients who began treatment were considered assessable for the primary and secondary end points. A Simon two-stage phase II minimax design was used (Simon, 1989) to evaluate the rate of progression-free survival at 6 months. The interim analysis was performed once enrolment into the first stage was completed. In the first stage, 23 patients were observed. If two or fewer patients had progression-free survival  $\geq 6$  months, the trial would be terminated early for lack of efficacy. If the progression-free survival of 3 or more of the first 23 patients was equal or greater than 6 months, then an additional 18 patients would be enrolled to a maximum of 41 patients. If eight or more of the 41 had PFS of at least 6 months, we would conclude that the treatment was efficacious. This design had a Type I error rate of 5% and a Type II error rate of 10% for the null hypothesis of a 6-month PFS rate of 10% vs the alternative of 27.5%. Kaplan–Meier estimates of survival, PFS, and duration of response were calculated with standard errors based on Greenwood's formula. These calculations were performed using the Proc Lifetest in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Patient recruitment and follow-up

From October 2005 to July 2007, 267 patients were assessed for eligibility (Figure 2). In all, 43 patients with advanced HCC and Child–Pugh A or B were enrolled in this study. The date of last patient follow-up is 9 June 2011. Of these, 20 patients (46.5%) had histological confirmation of HCC; 23 patients (53.5%) were

**Table 1** Treatments received by patients with advanced HCC before enrolment ( $n=41$ )

No previous treatment	7
Chemoembolisation	25
<sup>131</sup> I-Lipiodol	1
Octreotide	1
Percutaneous alcohol injection therapy	1
Surgery	9
Systemic chemotherapy or sorafenib	5

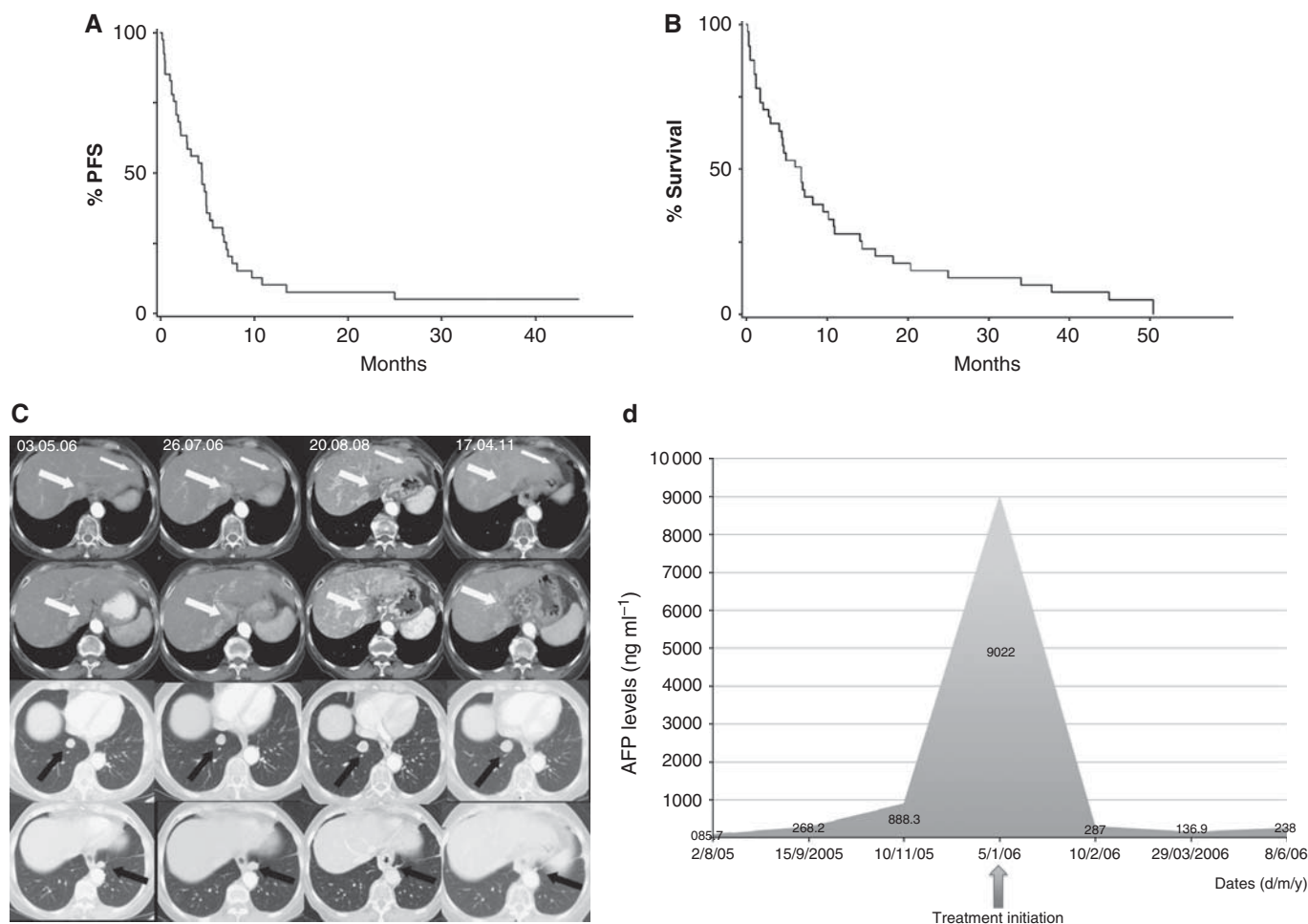
Abbreviation: HCC = hepatocellular carcinoma. Two patients had surgery and chemoembolisation, two patients had surgery and systemic chemotherapy, one patient had surgery and chemoembolisation and systemic chemotherapy, one patient had surgery and percutaneous alcohol injection, one patient had surgery and sorafenib, one patient had chemoembolisation and systemic chemotherapy and one patient had surgery and octreotide.

**Table 2** Patients' baseline characteristics

	No.	%
Age (years)		
Median age	64	
Range	18–85	
$\geq 65$	19	46.3
$< 65$	22	53.6
Sex		
Female	6	14.6
Male	35	85.4
ECOG performance status		
0	5	12.2
1	28	68.3
2	8	19.5
Child–Pugh status		
A5	15	36.6
A6	2	4.9
B7	6	14.6
B8	5	12.2
B9	11	26.8
No cirrhosis	2	4.9
BCLC status		
B	6	14.6
C	35	85.4
AFP > ULN		
Yes	28	68.3
No	13	16.7
Aetiology		
ETOH	2	4.9
Hepatitis B	6	14.6
Hepatitis B+C	1	2.4
Hepatitis C	22	53.7
ETOH+hepatitis C	1	2.4
NOS	9	22.0
Portal thrombosis	10	24.3
Extrahepatic disease		
Yes	16	39.0
Location		
Lung	6	14.6
Bone	3	7.3
Lymph nodes	4	9.8
Peritoneal carcinomatosis	1	2.4
Adrenal gland	1	2.4

Abbreviations: AFP =  $\alpha$ -fetoprotein; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; ETOH, ethyl alcohol; ULN, upper limit of normal.





**Figure 3** Progression-free and overall survival. **(A)** Median progression-free survival was 4.4 months (95% CI 2.1–5.3). **(B)** Median overall survival was 6.7 months (95% CI 3.0–10.2). **(C)** Long-term partial response in a patient with biopsy-proven hepatocellular carcinoma. A 76-year-old woman with hepatitis C and Child–Pugh A5, BCLC C, biopsy-proven hepatocellular carcinoma with bilateral pulmonary metastases, who had evidence of disease progression (+36% by Response Evaluation Criteria in Solid Tumours (RECIST) criteria) between 3 May 2006 (first column) and 26 July 2006 (second column) while enrolled in the SHARP study (Llovet *et al*, 2008b). Treatment with AM EMFs was initiated on 9 August 2006. Subsequent restaging multiphase contrast-enhanced computed tomographies (CTs) with images from corresponding levels (across rows) are demonstrated in the third and fourth columns over the course of 57 months. Note that the hypervascularity of the focal hepatic lesions (arrows in first two rows) became relatively hypoenhancing on arterial phase (20 August 2008). The patient developed main portal vein thrombosis with cavernous transformation as a complication of her cirrhosis. However, the intrahepatic lesion size is stable regardless of enhancement pattern. Note also that the left lung base lesion resolved (4th row), and the right lung base lesion remained stable (3rd row) over the duration of treatment. **(D)** Alpha-fetoprotein response in a 67-year-old patient with Child–Pugh A5, BCLC C HCC and hepatitis C (hepatitis B negative).

diagnosed based on elevated levels of  $\alpha$ -fetoprotein and characteristic imaging findings such as vascular invasion and characteristic differences in tumour blood flow. One patient was excluded because liver biopsy established the diagnosis of metastatic breast cancer. Another patient was excluded because of severely impaired liver function (Child–Pugh C11). These two patients who did not meet the inclusion criteria were registered as screening failures. Hence, a total of 41 patients were eligible to receive experimental therapy (Figure 2).

Two patients were lost to follow-up as they did not come back for their scheduled appointments. Repeated efforts were made to reach the patients and their families. The date of death of only one patient is known, and no information on response to treatment is available for either patient. Four patients withdrew consent while receiving therapy after 8.0, 9.3, 20.3, and 21.0 months, respectively (Figure 2). One patient elected to receive chemotherapy, one patient had poor treatment compliance as defined by administration of less than 50% of planned treatments at two consecutive return visits, one patient

elected to enrol in another experimental protocol, and one patient requested to be considered for liver transplantation as part of an extended indication, which does not fulfil the Milan criteria (Mazzaferro *et al*, 1996). This latter patient experienced disease progression and was ultimately not eligible for liver transplantation. Of the 35 patients who discontinued experimental therapy, four died of gastrointestinal bleeding, three of sepsis, three of hepatic failure, one of chronic obstructive pulmonary disease, two of chemotherapy- and chemoembolisation-related complications, and one of myocardial infarction (Figure 2). The remaining 24 patients discontinued because of disease progression assessed by imaging or significant clinical deterioration as assessed by the investigator (Figure 2). Estimated 60-day mortality was 27.8%; seven of 10 deaths were directly related to progression of disease. They were caused by liver failure in association with significant hepatic tumour involvement, without other cause of death, other than tumour involvement. Two deaths were secondary to gastrointestinal bleeding. One death was due to liver failure.

A total of 31 patients (75.6%) had radiological evidence of disease progression at the time of enrolment as defined by comparison of baseline imaging studies, with imaging studies obtained within the previous 6 months; 34 (82.9%) patients had received therapy before enrolment, five (14.6%) of them systemic chemotherapy or sorafenib (Table 1). Seven (17.1%) patients had not received therapy before enrolment for the following reasons: (1) severely impaired liver function in five cases; and (2) two patients refused to receive chemotherapy for metastatic disease. As shown in Table 2, the majority of patients had severely impaired liver function as demonstrated by the fact that 22 (53.7%) patients had Child–Pugh B disease and 35 (85.4%) BLCL stage C disease.

**Table 3** Independently reviewed best response (N = 41)

Best response	No.	%
Partial response <sup>a</sup>	4	9.8
Stable disease <sup>b</sup>	16	39.0
Progressive disease	8	19.5
Not available for response assessment	13	31.7

<sup>a</sup>Duration of the partial responses were +58.0, 46.9, 14.5 and 5.3 months (patient withdrew consent to undergo liver transplant). <sup>b</sup>To be classified as a stable disease, patients needed to have stable disease for  $\geq 12$  weeks.

## Treatment efficacy

Six of the first 23 patients (26.1%) had progression-free survival  $\geq 6$  months, which led us to continue enrolling patients up to the preplanned total of 41 patients (Figure 2). In total, 14 patients (34.1%) had SD for more than 6 months, which met our preplanned primary efficacy end point. Median progression-free survival was 4.4 months (95% CI 2.1–5.3) and median OS was 6.7 months (95% CI 3.0–10.2) (Figure 3A and B). One patient, previously enrolled in the SHARP study (Llovet *et al*, 2008b) and with evidence of disease progression at the time of enrolment, remains on therapy with a near complete response for 58 months (Figure 3C). Estimated survival at 12, 24 and 36 months is 27.9% (s.e. = 7.1%), 15.2% (s.e. = 5.7%), and 10.1% (s.e. = 4.8%), respectively. Subset analyses by Child–Pugh stage and accompanying figures are reported in Supplementary Information.

A total of 28 patients were evaluable for tumour response (Figure 2). Four (9.8%) patients had a partial response assessed with CT with or without contrast-enhanced ultrasound (Table 3). All partial responses were independently reviewed by two authors (MSR and DM). Three patients had biopsy-confirmed HCC and three had radiological evidence of disease progression at the time of enrolment (Table 4). Two patients had Child–Pugh A, one Child–Pugh B disease, and one had no cirrhosis. One of these

**Table 4** Characteristics of patients with either PR and/or long-term survival in excess of 24 months

Age at enrolment and sex	Race	Cause/cirrhosis (Child–Pugh)	Previous treatment/resection	AFP $\uparrow$ /pathology confirmation	Extra hepatic metastasis/portal thrombosis	BCLC	Okuda	CLIP	MELD	Progression before study entry/response	Treatment duration/overall survival (months)	Cause of death	Treatment received after completion of experimental therapy
62 M	Caucasian	Hep C/yes (A5)	Yes/no	Yes/yes	No/no	B	I	0	6	Yes/N/A	2.0/32.0	Tumour progressed	Systemic chemotherapy
67 F	Caucasian	Hep C/yes (B9)	Yes/no	Yes/yes	No/no	C	2	2	11	Yes/PR	11.7/11.7	GI bleed	None
30 M	Black	NOS/no	Yes/es	No/yes	No/no	B	N/A	N/A	N/A	No/PR	13.5/37.6	Tumour progressed	Chemoembolisation and systemic chemotherapy
61 M	Caucasian	Hep C/yes (A5)	Yes/no	No/no	No/no	C	I	I	6	Yes/SD	26.8/26.8	COPD	None
56 M	Caucasian	Hep B/C/yes (A5)	No/no	Yes/no	No/no	B	I	0	10	Yes/SD	4.9/50.3	Tumour progressed	Chemoembolisation
63 M	Caucasian	Hep C/yes (A5)	Yes/no	Yes/no	No/no	C	I	I	4	Yes/PR	4.9/14.3	Tumour progressed	None
76 F	Caucasian	Hep C/yes (A5)	No/no	No/no	No/yes	C	I	I	6	Yes/SD	44.6/44.6	Tumour progressed	None
76 F	Caucasian	Hep C/yes (A5)	No/yes	No/yes	Yes/yes	C	I	I	6	Yes/PR	+58.0/+58.0	On therapy	Still receiving experimental treatment

Abbreviations: AFP =  $\alpha$ -fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CLIP = Cancer Liver Italian Programme; GI = gastrointestinal; MELD = Model for end-stage liver disease; N/A = not applicable; PR = partial response; SD = stable disease.

**Table 5** Changes in AFP levels

Patient age and gender	AFP 6 months (ng ml <sup>-1</sup> )	Baseline AFP (ng ml <sup>-1</sup> )	8-week AFP (ng ml <sup>-1</sup> )	AFP variation (%)	Treatment duration (months)	End treatment status	Virus status
65 M	4.31	9.76	5.95	–39.0	3.0	Progression-death	HepC
67 F	888.3	9022.0	238.0	–97.3	11.7	GI bleed-death	HepC
64 M	4.7	4.5	2.6	–42.2	8.8	AMI-death	HepB
18 M	6.7	35.7	16.4	–55.7	7.8	Revoked consent-death	NOS

Abbreviations: AFP =  $\alpha$ -fetoprotein; AFP 6 months = AFP measured within 6 months before enrolment; AMI = acute myocardial infarction; baseline AFP = AFP at treatment initiation; GI = gastrointestinal; HepB = hepatitis B virus; HepC = hepatitis C virus; NOS = not otherwise specified; 8-week AFP = AFP at 8 weeks during treatment.

patients without biopsy-proven disease subsequently withdrew consent after 4.9 months to undergo liver transplantation. The patient died of progression of disease 9.4 months later before undergoing liver transplantation. One patient with Child–Pugh B disease had a partial response lasting 11.7 months and died of gastrointestinal bleeding. One patient died of disease progression at 44.6 months. Overall, there were six long-term survivors with an OS greater than 24 months and four long-term survivors with an OS greater than 3 years. Importantly, five of the six (83%) long-term survivors had radiological evidence of disease progression at the time of study enrolment (Table 4). Two of three patients with the longest survival (44.6 and +58 months) had radiological evidence of disease progression at the time of enrolment, BLCL stage C disease, as well as portal vein thrombosis, three predictors of short survival (Llovet *et al*, 2003). Serial AFP measurements, which predict radiological response and survival in patients with HCC (Chan *et al*, 2009; Riaz *et al*, 2009), were available for 23 patients. AFP decreased by 20% or more in four (9.8%) patients following initiation of therapy (Table 5). Figure 3D shows the time course of a 37-fold decrease in AFP in a patient who had a long-lasting (11.7 months) partial response as assessed by CT.

In all, 11 patients reported pain before treatment initiation, 3 patients reported grade 3, 5 patients reported grade 2, and 3 patients grade 1. Five patients reported complete disappearance of pain and two patients reported decreased pain shortly after treatment initiation. Two patients reported no changes and two patients reported increased pain. There were no treatment-related grade 2, 3, or 4 toxicities. The only treatment-related adverse events were grade 1 mucositis (one patient) and grade 1 somnolence (one patient) over a total of 266.8 treatment months.

## DISCUSSION

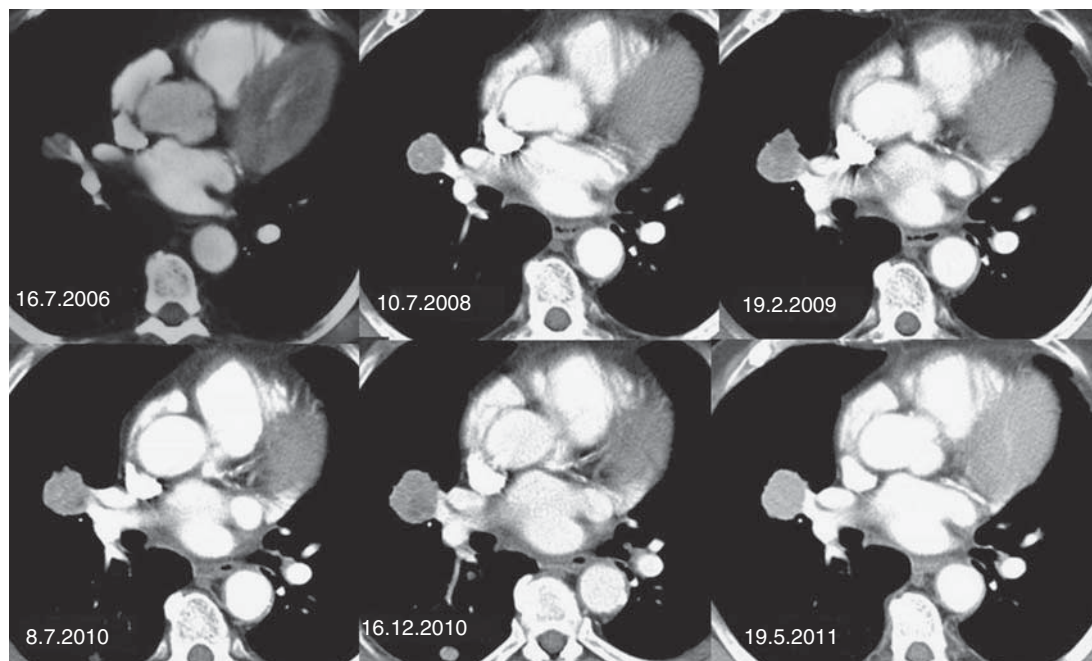
Treatment with AM EMFs did not show any significant toxicity despite long-term treatment. The lack of toxicity experienced by

the 41 patients presented in this report as well as the 28 patients from our previous report (Barbault *et al*, 2009) can be readily explained by the very low and safe levels of induced RF EMFs, which are more than 100 000 times lower than those delivered during RF ablation procedures (Chang, 2003). Hence, the putative mechanism of action of this novel therapeutic approach does not depend on temperature changes within the tumour.

These data are comparable to recent phase II studies evaluating the effectiveness of standard chemotherapy as well as novel targeted therapies in HCC (Abou-Alfa *et al*, 2006; Boige *et al*, 2007; Chuah *et al*, 2007; Cohn *et al*, 2008; Dollinger *et al*, 2008; Siegel *et al*, 2008). In a large phase II study assessing the effects of sorafenib in patients with HCC and Child–Pugh A and B who had not received previous systemic treatment, Abou-Alfa *et al* (2006) observed partial responses using the WHO criteria in 2.2% of patients. Investigator-assessed median time to progression was 4.2 months, and median OS was 9.2 months. Of note, all 137 patients from that study had evidence of disease progression after 14.8 months (Abou-Alfa *et al*, 2006), whereas, at the same time point, four (9.8%) of the patients enrolled in this study did not have evidence of disease progression. These findings suggest that RF AM EMF may increase the time to radiological progression in advanced HCC.

The majority of patients enrolled in this study had either failed standard treatment options or had severely impaired liver function that limited their ability to tolerate any form of systemic or intrahepatic therapy. Indeed, 16 patients (39.0%) had Child–Pugh B8 or B9 disease. Among these patients, the median progression-free survival was 4.4 months (95% CI 1.6–7.6 months), which is identical to that of the entire group. Five of these 16 patients (31.3%) received therapy for more than 7.5 months, which indicates that this therapy is well tolerated even in patients with severely impaired liver function.

Previous treatment with standard chemotherapy or sorafenib does not seem to impact the effectiveness of AM EMFs in the treatment of HCC. Indeed, three of the four patients who had a



**Figure 4** A 70-year-old man with recurrent thyroid cancer metastatic to the lungs: stable disease at 57.5 months. Long-term stable disease in a 70-year-old man with recurrent biopsy-proven thyroid carcinoma metastatic to the lungs enrolled in the previously published feasibility study (Barbault *et al*, 2009). Treatment with AM EMFs was initiated on 20 August 2006. As of 9 June 2011, the patient is asymptomatic and still receiving treatment with no evidence of disease progression. Images through the target metastatic lesion in the right hilum demonstrate minimal size change over the 4 years, given differences in computed tomography acquisition techniques over that time interval.



partial response while receiving AM EMFs had received previous systemic therapies (chemotherapy and sorafenib) and one had received intrahepatic therapy with  $^{131}\text{I}$ -lipiodol.

Tumour shrinkage as assessed by radiological imaging as well as changes in AFP levels were documented in patients with advanced HCC receiving RF EMF modulated at HCC-specific frequencies administered by an intrabuccal probe. Antitumour activity in patients with advanced HCC was exemplified by partial responses observed in four patients (9.8%) and decreases in AFP levels greater than 20% in four patients. A total of 18 patients (43.9%) either had objective response or SD  $\geq 6$  months.

Importantly, this therapeutic approach has long-lasting therapeutic effects in several patients with metastatic cancer. Two of these patients, one with recurrent thyroid cancer metastatic to the lungs (Figure 4) enrolled in our feasibility study (Barbault *et al*, 2009) and the patient shown in Figure 3C, are still receiving treatment without any evidence of disease progression and without side effects almost 5 years after being enrolled in these studies. These findings suggest that, in some patients, this therapeutic approach may achieve permanent control of advanced cancer with virtually no toxicity.

Our phase I/II study has several limitations. First, only 19 of the 41 patients had biopsy-proven HCC, and the others were diagnosed by clinical criteria, an approach similar to that used in a recently reported phase II trial evaluating the clinical and biological effects of bevacizumab in unresectable HCC (Siegel *et al*, 2008). Importantly, analysis restricted to these 19 patients shows rates of progression-free survival at 6 months, median progression-free survival and OS that are similar to those without biopsy-proven HCC (Supplementary Figures 1C and D). Furthermore, three of the four partial responses were observed in patients with biopsy-proven HCC. Hence, these findings strongly suggest that treatment with AM EMFs yields similar results in patients with

and without biopsy-confirmed HCC. Another potential limitation of our study consists in the use of contrast-enhanced ultrasound for the monitoring of some patients with HCC. It should be pointed out that recent studies indicate that the use of this imaging technique is comparable to that of CT scan with respect to the measurement of HCC tumours (Choi, 2007; Maruyama *et al*, 2008).

Antitumour response is considered the primary end point for phase II studies to proceed to further investigations. Studies applying Cox proportional hazards analysis indicate that this end point is consistently associated with survival in trials of locoregional therapies for HCC (Llovet *et al*, 2002) and a recent consensus article suggests that randomised studies are necessary to capture the true efficacy of novel therapies in HCC (Llovet *et al*, 2008a). In summary, the encouraging findings from this study warrant a randomised study to determine the impact of AM EMFs on OS and time to symptomatic progression.

## ACKNOWLEDGEMENTS

We thank Drs Al B Benson III, Northwestern University and Leonard B Saltz, Memorial Sloan-Kettering Cancer Center for reviewing the manuscript.

## Conflict of interest

AB and BP have filed a patent related to the use of electromagnetic fields for the diagnosis and treatment of cancer. AB and BP are founding members of TheraBionic LLC.

Supplementary Information accompanies the paper on British Journal of Cancer website (<http://www.nature.com/bjc>)

## REFERENCES

- Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De GJ, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB (2006) Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 24(26): 4293–4300
- Amato D, Pasche B (1993) An evaluation of the safety of low energy emission therapy (published erratum appears in *Compr Ther* 1994;20(12):681. *Compr Ther* 19: 242–247
- Barbault A, Costa F, Bottger B, Munden R, Bomholt F, Kuster N, Pasche B (2009) Amplitude-modulated electromagnetic fields for the treatment of cancer: discovery of tumor-specific frequencies and assessment of a novel therapeutic approach. *J Exp Clin Cancer Res* 28(1): 51
- Boige V, Raoul JL, Pignon JP, Bouche O, Blanc JF, Dahan L, Jouve JL, Dupouy N, Ducreux M (2007) Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. *Br J Cancer* 97(7): 862–867
- Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. *Hepatology* 42(5): 1208–1236
- Cance WG, Stewart AK, Menck HR (2000) The National Cancer Data Base Report on treatment patterns for hepatocellular carcinomas: improved survival of surgically resected patients, 1985–1996. *Cancer* 88(4): 912–920
- Chan SL, Mo FK, Johnson PJ, Hui EP, Ma BB, Ho WM, Lam KC, Chan AT, Mok TS, Yeo W (2009) New utility of an old marker: serial alpha-fetoprotein measurement in predicting radiologic response and survival of patients with hepatocellular carcinoma undergoing systemic chemotherapy. *J Clin Oncol* 27(3): 446–452
- Chang I (2003) Finite element analysis of hepatic radiofrequency ablation probes using temperature-dependent electrical conductivity. *Biomed Eng Online* 2: 12
- Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 10(1): 25–34
- Choi BI (2007) Doppler and harmonic ultrasound for hepatocellular carcinoma. *Hepatol Res* 37(Suppl 2): S172–S177
- Chuah B, Lim R, Boyer M, Ong AB, Wong SW, Kong HL, Millward M, Clarke S, Goh BC (2007) Multi-centre phase II trial of Thalidomide in the treatment of unresectable hepatocellular carcinoma. *Acta Oncol* 46(2): 234–238
- Cohn AL, Myers JW, Mamus S, Deur C, Nicol S, Hood K, Khan MM, Ilegbodu D, Asmar L (2008) A phase II study of pemetrexed in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 26(4): 381–386
- Dollinger MM, Behrens CM, Lesske J, Behl S, Behrmann C, Fleig WE (2008) Thymostimulin in advanced hepatocellular carcinoma: a phase II trial. *BMC Cancer* 8: 72
- ICNIRP (1998) Guidelines for limiting exposure to time-varying electric, magnetic and electromagnetic fields (up to 300 GHz). *Health Phys* 74: 494–522
- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. *Cancer J Clin* 61(2): 69–90
- Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. *Cancer J Clin* 60(5): 277–300
- Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ (2004) Cancer statistics, 2004. *Cancer J Clin* 54(1): 8–29
- Kassianides C, Kew MC (1987) The clinical manifestations and natural history of hepatocellular carcinoma. *Gastroenterol Clin North Am* 16(4): 553–562
- Kelly TL, Kripke DF, Hayduk R, Ryman D, Pasche B, Barbault A (1997) Bright light and LEET effects on circadian rhythms, sleep and cognitive performance. *Stress Med* 13: 251–258
- Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. *Lancet* 362(9399): 1907–1917
- Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ, for the Panel of Experts in HCC-Design Clinical Trials (2008a) Design and endpoints of



- clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 100(10): 698–711
- Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Sola R, Rodes J, Bruix J (2002) Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 359(9319): 1734–1739
- Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J, the SHARP Investigators Study Group (2008b) Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 359(4): 378–390
- Maruyama H, Yoshikawa M, Yokosuka O (2008) Current role of ultrasound for the management of hepatocellular carcinoma. *World J Gastroenterol* 14(11): 1710–1719
- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334(11): 693–700
- Pasche B, Erman M, Hayduk R, Mitler M, Reite M, Higgs L, Dafni U, Amato D, Rossel C, Kuster N, Barbault A, Lebet JP (1996) Effects of low energy emission therapy in chronic psychophysiological insomnia. *Sleep* 19: 327–336
- Pasche B, Erman M, Mitler M (1990) Diagnosis and management of insomnia. *N Engl J Med* 323: 486–487
- Pasche B, Barbault A (2003) Low-energy emission therapy: current status and future directions. In *Bioelectromagnetic Medicine*, Rosch PJ, Markov MS (eds) pp 321–327. Marcel Dekker Inc.: New York, NY
- Reite M, Higgs L, Lebet JP, Barbault A, Rossel C, Kuster N, Dafni U, Amato D, Pasche B (1994) Sleep inducing effect of low energy emission therapy. *Bioelectromagnetics* 15: 67–75
- Riaz A, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, Ibrahim SM, Sato KT, Baker T, Miller FH, Newman S, Omary R, Abecassis M, Benson III AB, Salem R (2009) Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *J Clin Oncol* 27(34): 5734–5742
- Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, Chen H, Clark-Garvey S, Weinberg A, Mandeli J, Christos P, Mazumdar M, Popa E, Brown RSJ, Rafii S, Schwartz JD (2008) Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 26(18): 2992–2998
- Simon R (1989) Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 10(1): 1–10
- Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 92(3): 205–216
- Thomas MB, Zhu AX (2005) Hepatocellular carcinoma: the need for progress. *J Clin Oncol* 23(13): 2892–2899



This work is licensed under the Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/3.0/>

# Cancer cell proliferation is inhibited by specific modulation frequencies

JW Zimmerman<sup>1</sup>, MJ Pennison<sup>1</sup>, I Brezovich<sup>2</sup>, N Yi<sup>3</sup>, CT Yang<sup>3</sup>, R Ramaker<sup>1</sup>, D Absher<sup>4</sup>, RM Myers<sup>4</sup>, N Kuster<sup>5</sup>, FP Costa<sup>6</sup>, A Barbault<sup>7</sup> and B Pasche<sup>\*,1</sup>

<sup>1</sup>Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham and UAB Comprehensive Cancer Center, 1802 6th Avenue South, NP 2566, Birmingham, AL 35294-3300, USA; <sup>2</sup>Department of Radiation Oncology, University of Alabama at Birmingham and UAB Comprehensive Cancer Center, Birmingham, AL 35294, USA; <sup>3</sup>Section of Statistical Genetics, Department of Biostatistics, School of Public Health, The University of Alabama at Birmingham, Birmingham, AL 35294, USA; <sup>4</sup>HudsonAlpha Institute for Biotechnology, Huntsville, AL 35806, USA; <sup>5</sup>ITIS Foundation, Swiss Federal Institute of Technology, Zurich, Switzerland; <sup>6</sup>Department of Transplantation and Liver Surgery, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil; <sup>7</sup>Rue de Verdun 20, Colmar 68000, France

**BACKGROUND:** There is clinical evidence that very low and safe levels of amplitude-modulated electromagnetic fields administered via an intrabuccal spoon-shaped probe may elicit therapeutic responses in patients with cancer. However, there is no known mechanism explaining the anti-proliferative effect of very low intensity electromagnetic fields.

**METHODS:** To understand the mechanism of this novel approach, hepatocellular carcinoma (HCC) cells were exposed to 27.12 MHz radiofrequency electromagnetic fields using *in vitro* exposure systems designed to replicate *in vivo* conditions. Cancer cells were exposed to tumour-specific modulation frequencies, previously identified by biofeedback methods in patients with a diagnosis of cancer. Control modulation frequencies consisted of randomly chosen modulation frequencies within the same 100 Hz–21 kHz range as cancer-specific frequencies.

**RESULTS:** The growth of HCC and breast cancer cells was significantly decreased by HCC-specific and breast cancer-specific modulation frequencies, respectively. However, the same frequencies did not affect proliferation of nonmalignant hepatocytes or breast epithelial cells. Inhibition of HCC cell proliferation was associated with downregulation of *XCL2* and *PLP2*. Furthermore, HCC-specific modulation frequencies disrupted the mitotic spindle.

**CONCLUSION:** These findings uncover a novel mechanism controlling the growth of cancer cells at specific modulation frequencies without affecting normal tissues, which may have broad implications in oncology.

British Journal of Cancer (2012) 106, 307–313. doi:10.1038/bjc.2011.523 www.bjcancer.com

Published online 1 December 2011

© 2012 Cancer Research UK

**Keywords:** hepatocellular carcinoma; electromagnetic fields; mitotic spindle; *PLP2*; *XCL2*

Treatment of hepatocellular carcinoma (HCC) is a major challenge given the limited number of therapeutic options available (Thomas and Zhu, 2005). We have developed a novel approach to treat advanced HCC, consisting of intrabuccal administration of very low levels of radiofrequency electromagnetic fields (RF EMF), amplitude-modulated at specific frequencies, and identified using biofeedback methods in patients with cancer (Barbault *et al*, 2009). The encouraging findings from a feasibility study (Barbault *et al*, 2009) led to the design of a phase I/II trial in patients with advanced HCC, and objective responses assessed by CT-scan and changes in alpha-fetoprotein levels were observed in several patients with biopsy-proven HCC (Costa *et al*, 2011). These findings prompted us to initiate reverse translational experiments to investigate the mechanism of action of amplitude-modulated electromagnetic fields. Two different *in vitro* exposure systems operating at 27.12 MHz were used to expose cells in culture, replicating patient-treatment conditions.

Proliferation of both HepG2 and Huh7 HCC cells was significantly decreased upon exposure to radiofrequency electromagnetic

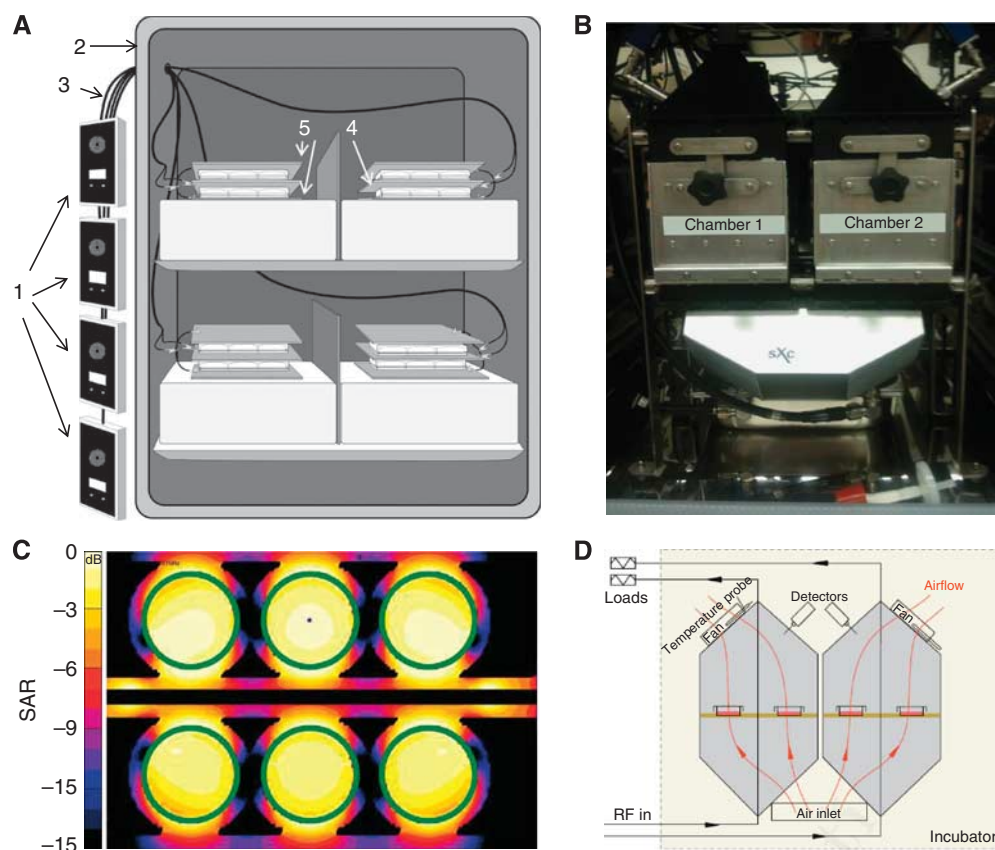
fields, which were modulated at HCC-specific modulation frequencies. To determine how such frequencies modulate cancer cell growth, we assessed differential gene expression with RNA-seq and found that the expression of several genes was significantly downregulated by HCC-specific modulation frequencies. Previous reports have shown that low intensity, intermediate frequency electric fields are capable of inhibiting cancer growth by interfering with the proper formation of the mitotic spindle (Kirson *et al*, 2004; Kirson *et al*, 2007). Similarly, we found that electromagnetic fields that are amplitude-modulated at HCC-specific frequencies disrupt the mitotic spindle of HCC cells. Thus, we provide novel evidence that very low level of amplitude-modulated electromagnetic fields block the growth of HCC cells in a tumour- and tissue-specific fashion.

## MATERIALS AND METHODS

### *In vitro* exposure devices

The design and construction of the two *in vivo* exposure devices (Figure 1) used to conduct these experiments is described in the Supplementary Information.

\*Correspondence: Dr B Pasche; E-mail: Boris.Pasche@ccc.uab.edu  
Received 10 October 2011; accepted 7 November 2011; published online 1 December 2011



**Figure 1** *In vitro* exposure experimental setups. **(A)** Parallel plate capacitor. Emitting devices (1) are placed outside the incubator (2). Each device is connected to a coaxial cable (3), which is connected to a set of brass plates inside the incubator. The centre brass plate (4) is connected to the inner conductor of the emitting device coaxial cable. The outer two brass plates (5) are connected to the outer conductor of the emitting device coaxial cable. Plates containing cells are placed in between the brass plates. **(B)** TEM cell. The system contains two identical TEM cells placed in an incubator. **(C)** Distribution of the specific absorption rate (SAR) of cell monolayer in the TEM cell (1 dB per contour). **(D)** Schematic representation showing the air flow through the TEM cell.

## Cell lines

HepG2 and Huh7 cells, both of Biosafety Level 1, were used as representative HCC cell lines. HepG2 cells were obtained from ATCC (Manassas, VA, USA), and Huh7 cells were a gift from Dr Nareej Saxena (Emory University). Normal hepatocytes, THLE-2 cells, were also obtained from ATCC. The breast adenocarcinoma cell line MCF-7 was used as a representative non-HCC malignant cell line (ATCC). The breast epithelial cell line MCF-10A (ATCC) was used to represent normal breast cells. Lymphoblastoid cell lines from healthy individuals enrolled in IRB-approved protocols were provided by Dr Jeff Edberg (UAB).

## [<sup>3</sup>H]thymidine incorporation assay

Growth inhibition (GI) was assessed in HCC cells exposed to HCC-specific modulation frequencies as previously described (Rosman *et al*, 2008).

## Luminescent cell viability assay

Cell proliferation was quantitated using the Promega CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison, WI, USA), a method to determine the number of viable cells in culture based on ATP quantitation.

## RNA-seq

We performed RNA-seq as previously described (Reddy *et al*, 2009). We used HepG2 cells exposed to either HCC-specific modulation frequencies or to randomly chosen frequencies. We double-selected polyA-containing mRNA from 3 µg of total RNA by using oligo-dT magnetic beads. We fragmented the mRNA with RNA fragmentation buffer and removed free-ions with a G-50 Sepharose spin column. Fragmented mRNA was used as a template to synthesise single-stranded cDNA with SuperScript II reverse transcriptase with random hexamer primers in the presence of RNaseOUT (Invitrogen by Life Technologies Corporation, Carlsbad, CA, USA). We synthesised double-stranded DNA (dsDNA) for sequencing by ligating Illumina (Illumina, San Diego, CA, USA) sequencing adaptors to blunted and dA-extended dsDNA, and size-selected fragments of 200–300 bp from a 2% Invitrogen gel and purified with a Qiagen Gel Extraction kit (Qiagen, Valencia, CA, USA). Lastly, we amplified the dsDNA library with 15 rounds of PCR with Illumina sequencing primers. Sequencing was performed on an Illumina GenomeAnalyzer IIX and the paired 36 bp reads were mapped to the hg18 reference genome by using ELAND (Illumina), allowing up to two mismatches per read and 10 or fewer map locations. By using the ERANGE software package (<http://woldlab.caltech.edu/rnaseq>), we placed uniquely mapped reads against 29 673 transcripts from NCBI build 36.1 of the human genome. After placing unique reads, ERANGE assigned multiple mapping reads and reads mapping to

splice junctions according to the number of unique reads in potential transcripts. Once all reads were mapped, ERANGE reported gene expression in units of reads per kilobase of exon and per million tags sequenced (RPKM).

### Quantitative PCR

At the conclusion of the AM-EMF exposure portion of the experiment, RNA extraction (Qiagen) and reverse transcription (TaqMan, Applied Biosystems by Life Technologies Corporation) were performed to generate cDNA. Experiments comparing gene expression in HCC cells receiving HCC-specific AM-EMF with gene expression in HCC cells not receiving any exposure were conducted using Applied Biosystems pre-designed TaqMan Gene Expression Assays (*PLP2*, cat#Hs01099969\_g1; *XCL2*, cat#Hs00237019\_m1; Applied Biosystems by Life Technologies Corporation). Real-time quantitation was completed in quadruplicate according to the manufacturer's instructions using an ABI 7900HT Real-Time PCR System (ABI by Life Technologies Corporation), with analysis performed using ABI SDS2.2 software. Quantitative values of gene expression were determined by comparing PCR amplification curves to a known standard curve generated in tandem with the experimental samples. Each sample was individually normalised to the average corresponding to endogenous expression of *GAPDH* (*GAPDH*, cat#Hs99999905\_m1, TaqMan, Applied Biosystems by Life Technologies Corporation). Averages of the normalised values from each condition were then used to compare the relative gene expression between the experimental groups. The s.e.m. was determined for each experimental condition.

### Confocal laser scanning microscopy

Cells undergoing mitosis were imaged using the Zeiss LSM 710 Confocal Laser Scanning Microscope (Carl Zeiss, Inc., Thornwood, NY, USA). For imaging experiments, 22 mm square microscope cover glass (Corning Life Sciences, Lowell, MA, USA, cat#2865–22) were flame-sterilised with 200-proof ethanol and placed in 6-well or 35 mm Falcon tissue culture plates (BD Biosciences, Franklin Lakes, NJ, USA). Approximately 300  $\mu$ l of cell suspension/growth media was added directly to the top of the cover slips, and cells were plated at varying concentrations ( $4 \times 10^5$ – $5 \times 10^5$  cells per ml) on separate cover slips for each assay to control for variability in antibody affinity between different experiments. Once the cells were given 8–18 h to attach to the cover slips, 3 ml of complete growth media was added to each well containing a cover slip. Following RF EMF exposure, indirect immunofluorescent microscopy compared the cells receiving HCC-specific modulation frequencies with cells not receiving any exposure (Microtubule Marker (AE-8) sc-73551, Fluorescent Secondary Alexa Fluor 488 goat anti-mouse IgG (H + L): A-11001; Santa Cruz Biotechnologies, Santa Cruz, CA, USA).

### Karyotype analysis

To determine whether these changes were associated with karyotypic changes, HepG2 cells exposed to HCC-specific modulation frequencies or unexposed were harvested, slides prepared, and metaphase chromosomes G-banded using standard methods. The chromosomes were analysed and the karyotype described according to the International System for Cytogenetic Nomenclature (Brothman *et al*, 2009).

### Statistical analyses

One sample two-sided *t*-test was performed to test the significance of cell proliferation exposed to RF EMF amplitude-modulated at tumour-specific or randomly chosen frequencies. ANCOVA analysis: For the long-term (7 weeks) GI analysis and the GI analysis for varying SAR values (0.05, 0.1, 0.4, and 1.0 W kg<sup>-1</sup>), data were fit to a linear model, and time point and dosage level were considered as covariates in determining significance.

## RESULTS

### Assessment of cell proliferation in the presence of RF EMF

Cell proliferation assays were conducted after 7 days, that is, 21 h of exposure to amplitude-modulated RF EMF. Treatment with HCC-specific modulation frequencies (Supplementary Table 1) significantly reduced the proliferation of HepG2 and Huh7 cells using both the parallel plate capacitor and the transverse electromagnetic (TEM) setups (Figure 1). The observed growth-inhibitory effect on HepG2 cells was of the same magnitude when using a tritium incorporation assay and a bioluminescence assay based on ATP consumption (Figure 2A). Having shown similar results with two different assays, the remainder of the cell proliferation experiments were conducted with the more commonly used tritium incorporation assay. Cell proliferation of HepG2 and Huh7 cells exposed to HCC-specific modulation frequencies was significantly lower than the proliferation of cells exposed either to randomly chosen frequencies (Supplementary Table 2) or not exposed to RF EMF (Figure 2A, columns 1–3). When HepG2 cells were exposed for only 1 h daily, we did not observe any significant inhibition of cell proliferation (Figure 2B). Daily exposure for 6 h instead of 3 h resulted in the same level of cell-proliferation inhibition (Figure 2B). To determine when HCC-specific modulation frequencies begin to exert anti-proliferative effects on HepG2 cells, we assessed cell proliferation following 3 days (9 h) of exposure and did not find any significant difference between cells exposed to HCC-specific modulation frequencies and unexposed cells (Figure 2B).

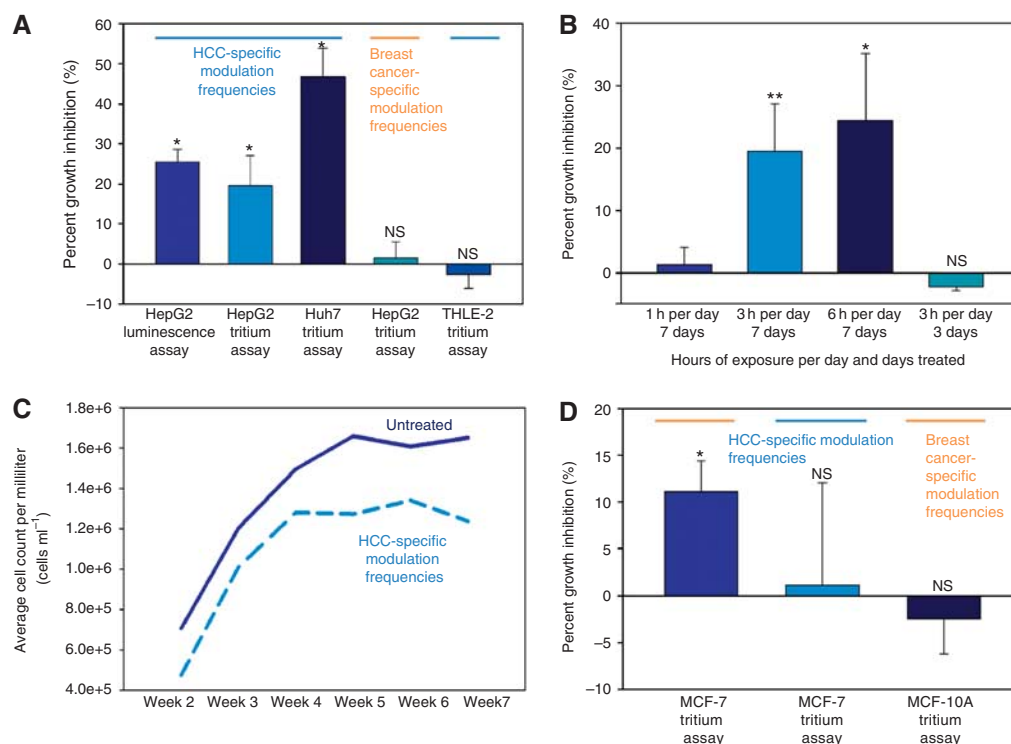
Further, to determine whether the growth-inhibitory effect of HCC-specific modulation frequencies persists over time and results in a decrease in the total number of tumour cells, we counted the number of HepG2 cells following treatment with HCC-specific modulation frequencies and that of untreated HepG2 cells weekly for up to 7 weeks. Cells that were either exposed to HCC-specific modulation frequencies or not exposed were split weekly at the same ratio over a period of 7 weeks. As shown in Figure 2C, when compared with unexposed HepG2 cells, the number of HepG2 cells following exposure to HCC-specific modulation frequencies decreased steadily over 7 weeks, resulting in a cumulative loss of  $1.71 \times 10^6$  cells per ml at week 7.

The average specific absorption rate (SAR) for cells exposed in the parallel capacitor plate system is 0.03 W kg<sup>-1</sup> (Supplementary Information). All initial experiments conducted with the TEM system were conducted at a SAR of 0.4 W kg<sup>-1</sup>. To determine the range of SARs within which significant GI was observed, additional cell proliferation experiments were performed at 0.05, 0.1 and 1.0 W kg<sup>-1</sup>. A significant anti-proliferative effect was observed at all SARs ranging from 0.05 to 1.0 W kg<sup>-1</sup> ( $P = 0.0354$ ). All subsequent assays with the TEM system were conducted at an SAR of 0.4 W kg<sup>-1</sup>.

### Inhibition of cell proliferation is tumour and tissue specific

Our previous clinical observations revealed that patients with HCC had biofeedback responses to specific modulation frequencies that were different from those identified in patients with other types of cancer, such as breast cancer (Barbault *et al*, 2009). To experimentally assess the relevance of these findings on the proliferation of tumour cells, we determined the specificity of frequencies identified in patients with these two tumour types given the documented objective clinical responses that included one complete and one partial response in two patients with metastatic breast cancer (Barbault *et al*, 2009) and three partial and one near-complete responses in four patients with HCC (Costa *et al*, 2011). A total of 194 breast cancer-specific modulation frequencies ranging in the same modulation frequency band from





**Figure 2** Cell proliferation assays of cell lines exposed to HCC-specific or breast cancer-specific modulation frequencies. **(A)** Cells were not split after initial seeding; medium was exchanged every 48 h. Experiments were performed with both equipment setups. Left to right columns: (1) HepG2 cells exposed to HCC-specific modulation frequencies with GI evaluated with a luminescence assay,  $25.46 \pm 3.22\%$  GI ( $P = 0.0009$ ). (2) HepG2 cells exposed to HCC-specific modulation frequencies with GI evaluated using tritium incorporation,  $19.44 \pm 7.60\%$  GI ( $P = 0.00993$ ). (3) Huh7 cells exposed to HCC-specific modulation frequencies,  $47.73 \pm 7.14\%$  GI ( $P = 0.018$ ). (4) HepG2 cells are not significantly inhibited when exposed to breast cancer-specific modulation frequencies,  $1.49 \pm 3.99\%$  GI ( $P = 0.8815$ ). (5) THLE-2 cells are not affected by HCC-specific modulation frequencies,  $-2.54 \pm 3.54\%$  GI ( $P = 0.6550$ ). Values represent average percent GI ( $n = 6$ )  $\pm$  %STERR. **(B)** Cell proliferation assays exposing cells for varying hours per day. Left to right: 1 h per day  $1.36 \pm 2.77\%$  ( $P = 0.8508$ ); 3 h per day  $19.44 \pm 7.60\%$  ( $P = 0.0099$ ); 6 h per day  $24.46 \pm 10.75\%$  ( $P = 0.0301$ ); 3 h per day for 3 days  $-2.12 \pm 0.66\%$  ( $P = 0.4067$ ). Values represent average percent GI ( $n = 6$ )  $\pm$  %STERR. **(C)** Cumulative decrease in cell counts over time when HepG2 cells are exposed to HCC-specific modulation frequencies. Samples were subcultured by volume every 7 days (1:20 split by volume). Average total cells mL<sup>-1</sup> per week: week 2:  $7.07 \times 10^5$ ,  $4.75 \times 10^5$ ; week 3:  $1.20 \times 10^6$ ,  $1.01 \times 10^6$ ; week 4:  $1.50 \times 10^6$ ,  $1.28 \times 10^6$ ; week 5:  $1.66 \times 10^6$ ,  $1.22 \times 10^6$ ; week 6:  $1.61 \times 10^6$ ,  $1.34 \times 10^6$ ; week 7:  $1.65 \times 10^6$ ,  $1.24 \times 10^6$  for untreated and treated samples, respectively. For the duration of the 7-week experiment with time considered as a covariate:  $P = 0.005751$ . **(D)** Left to right columns: (1) MCF-7 cells exposed to breast tumour-specific modulation frequencies,  $11.08 \pm 3.30\%$  GI ( $P = 0.0230$ ). (2) MCF-7 cells are not significantly inhibited when exposed to HCC-specific modulation frequencies,  $1.49 \pm 3.99\%$  ( $P = 0.8815$ ) GI, respectively. (3) MCF-10A cells are not affected by breast tumour-specific modulation frequencies,  $-2.46 \pm 3.75\%$  GI ( $P = 0.8579$ ). Values represent average percent GI ( $n = 6$ )  $\pm$  %STERR.

100 Hz to 21 kHz have been identified in patients with a diagnosis of breast cancer (Supplementary Table 3). In all 9 (4.6%) of the HCC-specific modulation frequencies are identical to breast cancer-specific modulation frequencies.

The two patients with metastatic breast cancer who had experienced an objective response to breast cancer-specific modulation frequencies had tumours that over-expressed oestrogen receptor (ER+) and progesterone receptor (PR+), but did not over-express ERBB2 (ERBB2-) (Barbault *et al*, 2009). We therefore chose the MCF-7 cell line as it represents the same tumour phenotype, that is, ER+, PR+, ERBB2-. Although the growth of MCF-10A breast cells was unaffected by exposure to breast cancer-specific modulation frequencies, exposure of MCF-7 breast cancer cells to breast cancer-specific modulation frequencies significantly inhibited cell proliferation (Figure 2D). However, exposure of HepG2 cells to the same breast cancer-specific modulation frequencies did not affect cell proliferation (Figure 2A). Similarly, the proliferation of MCF-7 cells was not affected by exposure to HCC-specific modulation frequencies (Figure 2D). Consequently, the observed anti-proliferative effect on HCC and breast cancer cells was observed only upon exposure to tumour-specific modulation frequencies previously identified in patients with a

diagnosis of HCC and breast cancer, respectively, despite the fact that more than 57% of the modulation frequencies only differed by <1% (Supplementary Tables 1 and 3).

Having demonstrated that the anti-proliferative effect of amplitude-modulated frequencies was tumour specific, we sought to determine whether the HCC-specific modulation frequencies have an effect on the proliferation of THLE-2 normal hepatocytes. As shown in Figure 2A, exposure of THLE-2 cells to HCC-specific modulation frequencies did not have any measurable effect on cell proliferation. These findings provide strong support for the novel notion that a combination of narrowly defined, specific modulation frequencies identified in a group of patients with the same type of cancer is capable of inhibiting cell proliferation in a tumour- and tissue-specific fashion.

### Tumour-specific modulation frequencies and gene regulation

To study the mechanism by which tumour-specific modulation frequencies inhibit cell proliferation, we assessed the gene expression profile of HepG2 cells exposed to HCC-specific modulation frequencies using RNA-seq, as it provides a more

comprehensive assessment of differential gene expression across a broader range of expression levels than microarray-based analysis (Wang *et al*, 2009). Overall, we did not observe statistically significant differences in transcript levels when comparing two HepG2 cultures exposed for 1 week, 3 h a day to HCC-specific modulation frequencies with two HepG2 cultures exposed to randomly chosen modulation frequencies (Supplementary Figure 1). However, we did observe a small number of genes with an absolute fold-change  $>1.5$  and a minimum mean RPKM of 1.5 following exposure to HCC-specific modulation frequencies. Two genes with an absolute fold-change  $>1.8$  appeared to be down-regulated in HepG2 cells exposed to HCC-specific modulation frequencies, *PLP2* and *XCL2*, and were considered to be candidates worthy of further experiments. We validated the downregulation of *PLP2* and *XCL2* with quantitative PCR in both HepG2 as well as Huh7 cells exposed to HCC-specific modulation frequencies (Figures 3A and B). There was no significant downregulation of *PLP2* and *XCL2* in MCF-7 breast cancer cells (Figure 3C). Similarly, there was no downregulation of *PLP2* and *XCL2* in nonmalignant cells, that is, in THLE-2 normal hepatocytes (Figure 3D), or in lymphoblastoid cell lines from healthy individuals (Figures 3E and F). These findings support the novel notion that the demodulation effects of RF EMF amplitude-modulated at specific frequencies inhibit cell proliferation and affect the expression of several genes in a tumour- and tissue-specific fashion.

### Tumour-specific modulation frequencies and disruption of the mitotic spindle

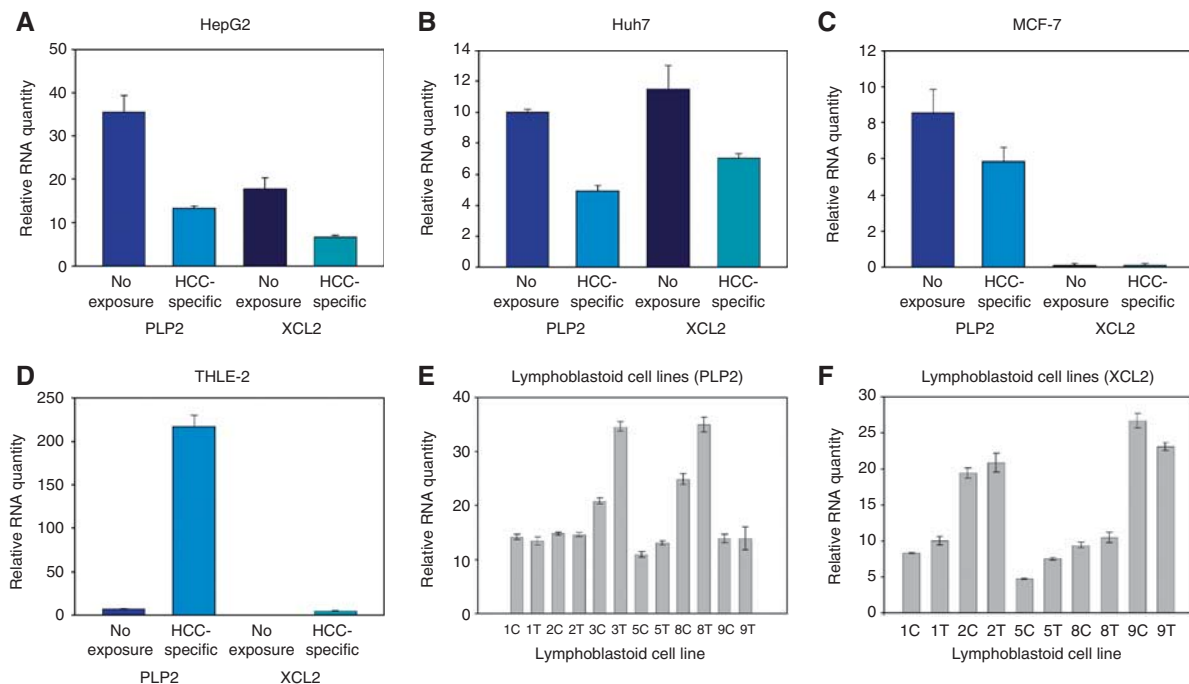
There is evidence that the proliferation of several rodent and human cancer cell lines is arrested by exposure to sinusoidal electric fields of  $100\text{--}200\text{ V m}^{-1}$  at a frequency of  $100\text{--}300\text{ kHz}$

(Kirson *et al*, 2004). This approach has also shown efficacy in animal and human tumour models as well as promising results in the treatment of patients with cancer (Kirson *et al*, 2004; Kirson *et al*, 2007; Salzberg *et al*, 2008; Kirson *et al*, 2009). The anti-tumour effect of this therapeutic approach appears to be caused by disruption of the mitotic spindle mediated by interference of spindle tubulin orientation and induction of dielectrophoresis (Kirson *et al*, 2004; Kirson *et al*, 2007). In contrast to the sinusoidal signals (Kirson *et al*, 2004), the carrier frequency of the signal applied in our experiments is more than 100 times higher; the peak E-field amplitude of the carrier at  $0.4\text{ W kg}^{-1}$  corresponds to approximately  $35\text{ V m}^{-1}$  inside the cell medium when the signal is sinusoidally amplitude-modulated at specific frequencies with 85% modulation depth (Kirson *et al*, 2004).

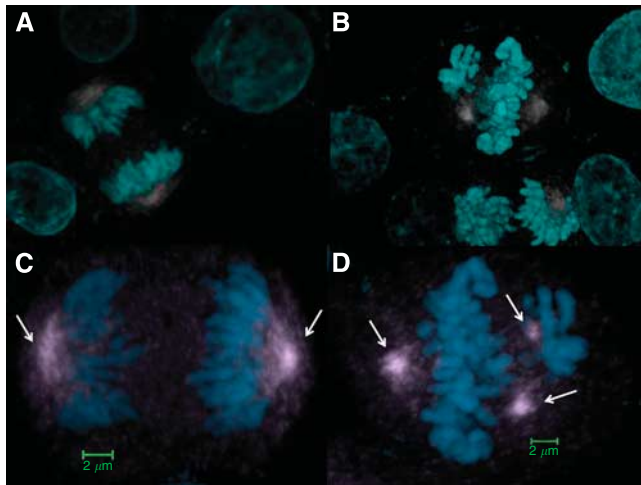
Despite these significant differences, confocal laser scanning microscopy revealed pronounced disruption of the mitotic spindle in more than 60% of HepG2 cells exposed for 1 week, 3 h per day to HCC-specific modulation frequencies whereas there was no disruption of the mitotic spindle in unexposed HepG2 cells (Figures 4A and B). Specifically, the observed cytoskeletal disruption in cells exposed to HCC-specific modulation frequencies was apparent in cells in mitosis, in which we saw centrosomal distortion and poor chromosomal separation at anaphase (Figure 4D). We found no evidence of karyotypic differences between HepG2 cells exposed to HCC-specific modulation frequencies and unexposed HepG2 cells.

### DISCUSSION

By exposing HCC cells to 27.12 MHz RF EMF sinusoidally amplitude-modulated at specific frequencies, which were previously



**Figure 3** Expression of *XCL2* and *PLP2* receiving HCC-specific RF EMF compared with cells not receiving exposure. **(A)** HepG2: *PLP2* ( $35.46 \pm 3.85$ ;  $13.17 \pm 0.70$ ) and *XCL2* ( $17.87 \pm 2.49$ ;  $6.52 \pm 0.48$ ) ( $P = 9.0371 \times 10^{-3}$  and  $P = 0.0179$ , respectively). **(B)** Huh7: *PLP2* ( $10.02 \pm 0.19$ ;  $4.95 \pm 0.35$ ) and *XCL2* ( $11.52 \pm 1.49$ ;  $7.02 \pm 0.29$ ) ( $P = 9.4981 \times 10^{-5}$  and  $P = 0.0536$ , respectively). **(C)** MCF-7: *PLP2* ( $8.52 \pm 1.30$ ;  $5.84 \pm 0.77$ ) and *XCL2* (levels not detectable). **(D)** THLE-2: *PLP2* ( $7.11 \pm 0.14$ ;  $216.89 \pm 13.18$ ) and *XCL2* ( $0.03 \pm 0.01$ ;  $4.55 \pm 1.04$ ) in THLE-2 cells exposed to HCC-specific modulation frequencies ( $P = 5.5108 \times 10^{-4}$  and  $P = 0.0221$ , respectively). **(E)** Expression levels of *PLP2* in lymphoblastoid cell lines (C = unexposed; T = HCC-specific exposure) (for all cell lines compiled  $P = 0.418$ ), LCL 3 expression was significant  $P = 0.0021$  as was LCL 8  $P = 0.0159$ . **(F)** Expression levels of *XCL2* in lymphoblastoid cell lines (for all cell lines compiled ( $P = 0.899$ ), LCL 1 expression difference was significant  $P = 0.0002$ ). Values represent average relative RNA expression ( $n = 4$ )  $\pm$  s.e.m. Levels were normalised to levels of GAPDH.



**Figure 4** Mitotic spindle disruption in cells receiving HCC-specific RF EMF compared with cells not receiving exposure. (A) HepG2 efficiently assembles a bipolar mitotic spindle, allowing cells to pass through the mitotic assembly checkpoint and successfully progress from metaphase to anaphase. (B) >60% of dividing HepG2 cells exposed to HCC-specific modulation frequencies exhibit microtubule-associated anomalies, (C) high magnification of unexposed HepG2 cells in mitosis (D) high magnification of HepG2 cells exposed to HCC-specific modulation frequencies shows errors such as tripolar spindle formation (Cyan = DAPI; Gray = Microtubules; Arrows = mitotic spindle).

identified in patients with a diagnosis of HCC (Barbault *et al*, 2009) and result in therapeutic responses in patients with HCC (Costa *et al*, 2011), we demonstrate a robust and sustained anti-proliferative effect. This effect was seen within SARs ranging from 0.03 to 1.0 W kg<sup>-1</sup>, that is, within the range of exposure in humans receiving treatment administered intrabuccally (Barbault *et al*, 2009; Costa *et al*, 2011). HCC-specific modulation frequencies began to hinder cell proliferation after 7 days of exposure and the anti-proliferative effect increased over a 7-week period. The anti-proliferative effect HCC-specific modulation frequencies were observed only in HCC cells, but not in breast cancer cells or normal hepatocytes.

The specificity of modulation frequencies is exemplified by the fact that two sets of similar modulation frequencies (breast cancer-specific and randomly chosen) within the same range, that is, from 100 Hz to 21 kHz, did not affect the proliferation of HCC cells. Similarly, the proliferation of breast cancer cells was affected only by breast cancer-specific modulation frequencies, but neither by HCC-specific nor by randomly chosen modulation frequencies. The fact that >50% of the modulation frequencies from these three programs differed by <1%, provides strong experimental evidence that the biological effects are only mediated by a combination of narrowly defined, tumour-specific modulation frequencies.

The modulation-frequency specific laboratory findings are consistent with the clinical observation of a complete response in a patient with breast cancer metastasis to the adrenal gland and the bone while a primary malignancy of the uterus continued to grow (Barbault *et al*, 2009). This suggests that a combination of precise tumour-specific modulation frequencies is needed to block cancer growth *in vitro* and in patients with a diagnosis of cancer. The clinical results reported by Barbault *et al*, (2009) and Costa *et al*, (2011) as well as laboratory evidence included in this report provide support for the novel and transformational concept that the growth of human tumours arising from the same primary tissue may be effectively blocked by identical modulation

frequencies. While receiving treatment with HCC-specific modulation frequencies, one black and three white patients with advanced carcinoma had partial responses (Costa *et al*, 2011). Furthermore, proliferation of the Huh7 HCC cell line, which is derived from a Japanese patient's tumour (Nakabayashi *et al*, 1982), exhibited the most pronounced response to HCC-specific modulation frequencies (Figure 2A). This indicates that the frequency signature and biological effects of HCC-specific modulation frequencies are likely independent of ethnic status.

There is no known biophysical mechanism accounting for the effect observed in these experiments; however, other modulation-frequency dependent effects have been observed in biological systems at similarly low exposure levels. Documented effects have occurred in cellular processes controlling cell growth, proliferation, and differentiation (Blackman, 2009). Further, modulation of the signal appears to be a critical factor in the response of biological systems to electromagnetic fields (Blackman, 2009). The amount of electromagnetic energy delivered is far too low to break chemical bonds or cause thermal effects, necessitating alternative mechanistic explanations for observed biological outcomes. Several theories have been put forth to explain biological responses to electromagnetic fields. Some reports have shown that low levels of electromagnetic fields can alter gene expression and subsequent protein synthesis by interaction of the electromagnetic field with specific DNA sequences within the promoter region of genes (Blank and Goodman, 2008; Blank and Goodman, 2009). Such changes have been demonstrated in the family of 'heat shock' proteins that function in the cell stress response (Blank and Goodman, 2009).

To thoroughly interrogate gene expression changes in cells exhibiting decreased cell proliferation, we used high-throughput sequencing technologies to sequence the cells' cDNA, a technique that has become invaluable in the study of cancer (Maher *et al*, 2009). Tumour cell G1 was associated with downregulation of *PLP2* and *XCL2* as well as with disruption of the mitotic spindle. *PLP2* encodes an integral membrane protein that localises to the endoplasmic reticulum in epithelial cells. The encoded protein can multimerise and may function as an ion channel (Breitwieser *et al*, 1997). *PLP2* enhances chemotaxis of human osteogenic sarcoma cells (Lee *et al*, 2004) and *PLP2* downregulation is associated with decreased metastasis in a mouse model of cancer (Sonoda *et al*, 2010). *XCL2* encodes for a protein that enhances chemotactic activity for lymphocytes and downregulation of *XCL2* has been shown to be associated with good prognosis in patients with breast cancer (Teschendorff *et al*, 2007; Teschendorff and Caldas, 2008). The pronounced disruption of the mitotic spindle seen in the majority of HepG2 cells exposed to HCC-specific modulation frequencies undergoing mitosis is not associated with karyotypic changes, but may be a major determinant of the anti-tumour effects of HCC-specific modulation frequencies accounting for the therapeutic responses seen in patients receiving the same modulation frequencies (Costa *et al*, 2011).

Exposure of HCC cells to the same RF EMF modulated at slightly different modulation frequencies did not result in changes in gene expression, which demonstrates that inhibition of cell proliferation is associated with changes in gene expression levels.

In conclusion, we show that very low levels of 27.12 MHz radiofrequency electromagnetic fields, which are comparable to the levels administered to patients, inhibit tumour cell growth when modulated at specific frequencies. The exciting findings presented in this report suggest that the anti-proliferative effect of modulation frequencies is both tumour- and tissue-specific, and is mediated by changes in gene expression as well as disruption of the mitotic spindle. These findings uncover a new alley to control tumour growth and may have broad implications for the treatment of cancer.

## ACKNOWLEDGEMENTS

We thank Dr Carl F. Blackman, 3413 Horton Street, Raleigh, NC, Dr Richard B. Marchase, UAB, and Dr Bernard Veyret, University of Bordeaux for reviewing the manuscript. We also thank Dr Andrew Carroll, Cytogenetics Laboratory, UAB Department of Genetics, for performing the karyotype analysis. We would also like to thank Dr Jeff Edberg for the lymphoblastoid cell lines

from the UAB Control Population. Finally, we would like to thank Dr Nareej Saxena, Emory University for his expertise and the gift of Huh7 cells.

Supplementary Information accompanies the paper on British Journal of Cancer website (<http://www.nature.com/bjc>)

## REFERENCES

- Barbault A, Costa F, Bottger B, Munden R, Bomholt F, Kuster N, Pasche B (2009) Amplitude-modulated electromagnetic fields for the treatment of cancer: discovery of tumor-specific frequencies and assessment of a novel therapeutic approach. *J Exp Clin Cancer Res* **28**(1): 51
- Blackman C (2009) Cell phone radiation: evidence from ELF and RF studies supporting more inclusive risk identification and assessment. *Pathophysiology* **16**: 205–216
- Blank M, Goodman R (2008) A mechanism for stimulation of biosynthesis by electromagnetic fields: charge transfer in DNA and base pair separation. *J Cell Physiol* **214**: 20–26
- Blank M, Goodman R (2009) Electromagnetic fields stress living cells. *Pathophysiology* **16**: 71–78
- Breitwieser GE, McLenithan JC, Cortese JF, Shields JM, Oliva MM, Majewski JL, Machamer CE, Yang VW (1997) Colonic epithelium-enriched protein A4 is a proteolipid that exhibits ion channel characteristics. *Am J Physiol* **272**(3 Pt 1): C957–C965
- Brothman AR, Persons DL, Shaffer LG (2009) Nomenclature evolution: changes in the ISCN from the 2005 to the 2009 edition. *Cytogenet Genome Res* **127**: 1–4
- Costa FP, de Oliveira AC, Meirelles R, Machado MCC, Zanesco T, Surjan R, Chammas MC, de Souza Rocha M, Morgan D, Cantor A, Zimmerman J, Brezovich I, Kuster N, Barbault A, Pasche B (2011) Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. *Br J Cancer* **105**(5): 640–648
- Kirson ED, Dbaly V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, Mordechovich D, Steinberg-Shapira S, Gurvich Z, Schneiderman R, Wasserman Y, Salzberg M, Ryffel B, Goldsher D, Dekel E, Palti Y (2007) Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *PNAS* **104**(24): 10152–10157
- Kirson ED, Giladi M, Gurvich Z, Itzhaki A, Mordechovich D, Schneiderman RS, Wasserman Y, Ryffel B, Goldsher D, Palti Y (2009) Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs. *Clin Exp Metastasis* **26**(7): 633–640.
- Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, Schatzberger R, Palti Y (2004) Disruption of cancer cell replication by alternating electric fields. *Cancer Res* **64**(9): 3288–3295
- Lee SM, Shin H, Jang SW, Shim JJ, Song IS, Son KN, Hwang J, Shin YH, Kim HH, Lee CK, Ko J, Na DS, Kwon BS, Kim J (2004) PLP2/A4 interacts with CCR1 and stimulates migration of CCR1-expressing HOS cells. *Biochem Biophys Res Commun* **324**: 768–772
- Maher CA, Kumar-Sinha C, Cao X, Kalyana-Sundaram S, Han B, Jing X, Sam L, Barrette T, Palanisamy N, Chinnaiyan AM (2009) Transcriptome sequencing to detect gene fusions in cancer. *Nature* **458**(7234): 97–101, doi:10.1038/nature07638
- Nakabayashi H, Taketa K, Miyano K, Yamane T, Sato J (1982) Growth of human hepatoma cell lines with differentiated functions in chemically defined medium. *Cancer Res* **42**: 3858–3863
- Reddy TE, Pauli F, Sprouse RO, Neff NF, Newberry KM, Garabedian MJ, Myers RM (2009) Genomic determination of the glucocorticoid response reveals unexpected mechanisms of gene regulation. *Genome Res* **19**(12): 2163–2171
- Rosman DS, Phukan S, Huang CC, Pasche B (2008) TGFBR1\*6A enhances the migration and invasion of MCF-7 breast cancer cells through RhoA activation. *Cancer Res* **68**(5): 1319–1328
- Salzberg M, Kirson E, Palti Y, Rochlitz C (2008) A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie* **31**(7): 362–365.
- Sonoda Y, Warita M, Suzuki T, Ozawa H, Fukuda Y, Funakoshi-Tago M, Kasahara T (2010) Proteolipid protein 2 is associated with melanoma metastasis. *Oncol Rep* **23**: 371–376
- Teschendorff AE, Caldas C (2008) A robust classifier of high predictive value to identify good prognosis patients in ER-negative breast cancer. *Breast Cancer Res* **10**(4): R73.
- Teschendorff AE, Miremadi A, Pinder SE, Ellis IO, Caldas C (2007) An immune response gene expression module identifies a good prognosis subtype in estrogen receptor negative breast cancer. *Genome Biol* **8**(8): R157.
- Thomas MB, Zhu AX (2005) Hepatocellular carcinoma: the need for progress. *J Clin Oncol* **23**(13): 2892–2899
- Wang Z, Gerstein M, Snyder M (2009) RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet* **10**: 57–63

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License.



Medical Treatments & Modulation; Treating cancer  
with amplitude-modulated electromagnetic fields: a  
potential paradigm shift, again? British Journal of Cancer.  
(Dr. Carl Blackman); 2012

## Editorial

# Treating cancer with amplitude-modulated electromagnetic fields: a potential paradigm shift, again?

CF Blackman<sup>\*,1</sup>

<sup>1</sup>Integrated Systems Toxicology Division (B-105-03), US Environmental Protection Agency, Research Triangle Park, NC 27711, USA

British Journal of Cancer (2012) 106, 241–242. doi:10.1038/bjc.2011.576 www.bjancer.com  
© 2012 Cancer Research UK

The Zimmerman *et al* (2012) study published here, coupled with the group's two preceding papers (Barbault *et al*, 2009; Costa *et al*, 2011), identify a potential modality for treating tumours at a dramatic reduction in trauma and cost. This set of clinical and explanatory laboratory results should be understood in the context of the history of research into the biological effects of electromagnetic fields (EMFs).

The most successful clinical application is the use of EMF to initiate fusion in fractured long bones that would not otherwise heal. Pulsed fields were designed to simulate the natural piezoelectric signals generated from bones under varying stress while walking (e.g., Bassett, 1985). There are also other reports that EMF can reduce pain and stimulate wound healing after surgery.

The group's two previous clinical reports were critical to the design of this new Zimmerman *et al* study. Barbault *et al* (2009) described how they obtained the specific frequencies for different tumour diagnoses, which are then used in the amplitude-modulated (AM)-EMF treatment of those patients to stabilise the disease beyond normal expectations. Costa *et al* (2011) reported surprising clinical benefits from using the specific AM-EMF signals to treat advanced hepatocellular carcinoma, stabilising the disease and even producing partial responses up to 58 months in a subset of the patients. Now Zimmerman *et al* have examined the growth rate of human tumour cell lines from liver and breast cancers along with normal cells from those tissues exposed to AM-EMF. Reduced growth rate was observed for tumour cells exposed to tissue-specific AM-EMF, but no change in growth rate in normal cells derived from the same tissue type, or in tumour or normal cells from the other tissue type. The growth rate inhibitory response was field-strength (SAR) and exposure-time dependent. In ancillary tests, they observed reduction in gene expression and increases in mitotic spindle dysfunction only for the AM-EMF exposure that reduced the cell growth rate.

The work of Zimmerman *et al*, Costa *et al* and Barbault *et al* was not done in a vacuum. More than 30 years ago, Suzanne Bawin working in Ross Adey's lab (Bawin *et al*, 1975), with independent replication by my group (Blackman *et al*, 1979), demonstrated that biological effects could be caused by certain AM frequencies on a carrier wave but not other frequencies, similar to the current work. Subsequent reports in the 1980s by several groups continued to support and extend the initial findings (Adey, 1992; Blackman, 1992).

This growing collection of reports demonstrating AM-EMF-induced biological effects led to recognition by national and international authorities that this modality needed to be

considered in hazard evaluation, in addition to field-induced heating as a cause for health concern. The National Council on Radiation Protection and Measurements (1986) recommended a reduction in the allowable exposure intensity limits for AM radiation above a certain level, and the World Health Organization (1993) explicitly acknowledged AM as a future issue to be examined in setting exposure guidelines. Unexpectedly, research funding for this area dried up around 1990 and scientific advances dramatically slowed. A promising area of research fell by the wayside.

The Zimmerman *et al* paper, providing essential laboratory data to support the two previous clinical treatment papers, has resurrected the promising AM-EMF paradigm. It should lead to a major reevaluation of this novel and potentially effective treatment for cancer and possibly other conditions. This study demonstrates the fundamental requirement for a biological 'information content' code (i.e., the AM spectral profile, much like different AM radio stations with different content – e.g., all news, or music) that can affect tumour cells from the tissue of origin, while apparently being ignored by normal cells from various tissues and tumour cells from different tissues of origin. The correspondence between AM-EMF-induced effects on cell proliferation, gene expression, and mitotic spindle dysfunction provide some clues to a possible biological mechanism of action.

The tools developed in Barbault *et al* (2009) to identify relevant treatment frequencies can be seen to have direct clinical and medical relevance in determining the characteristics of a new modality that may prove useful in cancer treatment. The precision of the frequency definitions, down to 1 mHz, is very unusual, but it is reminiscent of the biological effects reported for 40–48-GHz frequencies by Grundler *et al* (1982), and may represent a true effective frequency limitation that most studies would have missed, because of the lack of available, precise generation equipment or lack of the investigator knowledge.

The Zimmerman *et al* study raises a number of issues to be resolved. First, a more detailed elucidation of AM-EMF-induced genomic pathway changes is needed in order to put the results on a firmer mechanistic basis. Second, more information is needed on the nature of the growth inhibition, for example, is it persistent or do resistant cells emerge from continued treatment? Third, will cells from liver or breast tissues in different stages of transformation reduce or enhance sensitivity to AM-EMF exposure? Fourth, will tissue-specific AM-EMF tumour treatments for humans have similar effects on cells from animal tumours? For example, if rodent liver tumour cells respond similarly to the treatments, this may open a new, more rapid investigation of the therapeutic efficacy of the technique.

\*Correspondence: Dr CF Blackman; E-mail: Blackman.Carl@epa.gov

When the three studies are taken together, it is apparent that there are gaps in knowledge that can limit the acceptance of this treatment for cancer. How do the biofeedback endpoints (skin electrical resistance, pulse amplitude and blood pressure) engage with the disease state to provide an indication of effective frequencies to treat patients, and most surprisingly, to directly affect tumour cells *in vitro* from the same tissue type? The issue of frequency precision in the AM-EMF signal also needs to be examined and characterised as a function of different physiological growth conditions. Equally mysterious is the mechanism by which AM-EMF administered via a spoon-shaped antenna placed in the mouth can influence cancer cells in the liver or breast of patients. Finally, these patients had advanced cancer and were in palliative care when EMF testing began. Would earlier intervention in breast cancer or liver cancer cases with AM-EMF prove to be more effective?

Funding is needed for further medical and basic science research to identify and characterise the biological influence that amplitude-modulated EMFs have on the body, in its normal state, when recovering from disease or injury, and when initially affected

by disease. As a caution, 'information content' EMF signals may not always have beneficial consequences for humans or their environment, so research should examine potential detrimental biological outcomes as well.

The group of three papers demonstrate a new, potentially important modality in the treatment of cancer that could lead to a paradigm shift in disease treatment. I hope that this medical application of AM-EMF will not be allowed languish without funding, as happened with its previous, ill-fated emergence.

### Disclaimer

This commentary has been subjected to review by the National Health and Environmental Effects Research Laboratory, and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

### REFERENCES

- Adey RW (1992) Collective properties of cell membranes. In *Interaction Mechanisms of Low-level Electromagnetic Fields in Living Systems*, Norden B, Ramel C (eds) pp 47–77. Oxford University Press: Oxford; New York
- Barbault A, Costa FP, Bottger B, Munden RF, Bomholt F, Kuster N, Pasche B (2009) Amplitude-modulated electromagnetic fields for the treatment of cancer: discovery of tumor-specific frequencies and assessment of a novel therapeutic approach. *J Exp Clin Cancer Res* 28: 51–60
- Bassett CA (1985) The development and application of pulsed electromagnetic fields (PEMFs) for ununited fractures and arthrodeses. *Clin Plast Surg* 12: 259–277
- Bawin SM, Kaczmarek LK, Adey WR (1975) Effects of modulated VHF fields on the central nervous system. *Ann N Y Acad Sci* 247: 74–81
- Blackman CF (1992) Calcium release from nervous tissue: experimental results and possible mechanisms. In *Interaction Mechanisms of Low-Level Electromagnetic Fields in Living Systems*, Norden B, Ramel C (eds), pp 107–129. Oxford University Press: Oxford; New York
- Blackman CF, Elder JA, Weil CM, Benane SG, Eichinger DC, House DE. (1979) Induction of calcium ion efflux from brain tissue by radio-frequency radiation: effects of modulation-frequency and field strength. *Radio Sci* 14(6S): 93–98
- Costa FP, de Oliveira AC, Meirelles R, Machado MC, Zanesco T, Surjan R, Chammas MC, de Souza Rocha M, Morgan D, Cantor A, Zimmerman J, Brezovich I, Kuster N, Barbault A, Pasche B. (2011) Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. *Br J Cancer* 105: 640–648
- Grundler W, Keilmann F, Putterlik V, Strube D (1982) Resonant-like dependence of yeast growth rate on microwave frequencies. *Br J Cancer Suppl* 5: 206–208
- National Council on Radiation Protection and Measurements (1986) Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields. pp 382, NCRP Report No. 86, NCRP: Bethesda, MD
- World Health Organization (1993) Environmental Health Criteria 137. "Electromagnetic Fields (300Hz to 300 GHz)". pp 290, Geneva
- Zimmerman ZW, Pennison MJ, Brezovich I, Nengun Y, Yang CT, Ramaker R, Absher D, Myers RM, Kuster N, Costa FP, Barbault A, Pasche B (2012) Cancer cell proliferation is inhibited by specific modulation frequencies. *Br J Cancer* 106: 307–313

Modulation; Dr. Alan Frey PhD., Comments, Feb. 7, 2013

**Before the  
Federal Communications Commission  
Washington, D.C. 20554**

In the Matter of	)	
	)	
Notice of Proposed Rulemaking	)	
18 FCC Rcd 13187, 13188 ¶1 (2003)	)	ET Docket No. 03-137
	)	
And	)	
	)	
Service Rules for the Advanced Wireless Services	)	WT Docket No. 12-357
H Block---Implementing Section 6401 of the	)	
Middle Class Tax Relief and Job Creation Act of	)	
2012 Related to the 1915-1920 MHz and	)	
1995-2000 MHz Bands ¶53 footnote 95	)	

To: Office of the Secretary  
Federal Communications Commission  
Washington, DC 20554

Comment Filed by:

Allan H. Frey  
11049 Seven Hill Lane  
Potomac, MD 20854 USA

Email: [allan@freys.us](mailto:allan@freys.us)  
Voice: 301.299.5181  
Fax: 703.226.2261

February 5 , 2013

## **AFFIDAVIT OF Allan H. Frey**

I Allan H. Frey, attest that my statements are true to the best of my knowledge.

1. My name is Allan H. Frey

**Comment** round for ET Docket No. 03-137 and WT Docket No. 12-357.

2. My address is 11049 Seven Hill Lane, Potomac, MD 20854 USA  
Email: allan@freys.us
3. I am a scientist with a considerable amount of experience in research on the biomedical effects of the non-ionizing radiation being considered here by the FCC.
4. The issue is not whether cell phones are safe; it is whether the particular frequencies and modulations that the FCC assigned to cell phones, based on faulty assumptions, are safe.
5. The FCC made assumptions about physiology and about available biological data with non-ionizing radiation. It then assigned frequencies and modulations for use with cell phones, in part, based on those assumptions; assumptions which are not valid.
6. The two attached articles that have been published in the scientific literature indicate the nature of the problem with the FCC's decision making regarding cell phones ("Cell phone health risk" and "On the safety of cell phone radiation"). There are many more articles, by me and others, that are available in the scientific literature that show that the FCC's assumptions are not justified. Thus, the FCC has placed the Public at risk in what amounts to a grand experiment with their health, without their informed consent.

  
Allan H. Frey

February 5, 2013

Modulation; Real Versus Simulated Mobile Phone Exposures in  
Experimental Studies. Biomed Res Int. (Prof. Panagopoulos et al); 2015



## Review Article

# Real versus Simulated Mobile Phone Exposures in Experimental Studies

Dimitris J. Panagopoulos,<sup>1,2,3</sup> Olle Johansson,<sup>4</sup> and George L. Carlo<sup>5</sup>

<sup>1</sup>National Center for Scientific Research “Demokritos”, 60037 Athens, Greece

<sup>2</sup>Department of Biology, University of Athens, 15784 Athens, Greece

<sup>3</sup>Radiation and Environmental Biophysics Research Centre, 11143 Athens, Greece

<sup>4</sup>Experimental Dermatology Unit, Department of Neuroscience, Karolinska Institute, 171 77 Stockholm, Sweden

<sup>5</sup>The Science and Public Policy Institute, Institute for Healthful Adaptation, Falls Church, VA 22044, USA

Correspondence should be addressed to Dimitris J. Panagopoulos; [dpanagop@biophysics.gr](mailto:dpanagop@biophysics.gr)

Received 20 February 2015; Accepted 14 July 2015

Academic Editor: Sabrina Angelini

Copyright © 2015 Dimitris J. Panagopoulos et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We examined whether exposures to mobile phone radiation in biological/clinical experiments should be performed with real-life Electromagnetic Fields (EMFs) emitted by commercially available mobile phone handsets, instead of simulated EMFs emitted by generators or test phones. Real mobile phone emissions are constantly and unpredictably varying and thus are very different from simulated emissions which employ fixed parameters and no variability. This variability is an important parameter that makes real emissions more bioactive. Living organisms seem to have decreased defense against environmental stressors of high variability. While experimental studies employing simulated EMF-emissions present a strong inconsistency among their results with less than 50% of them reporting effects, studies employing real mobile phone exposures demonstrate an almost 100% consistency in showing adverse effects. This consistency is in agreement with studies showing association with brain tumors, symptoms of unwellness, and declines in animal populations. Average dosimetry in studies with real emissions can be reliable with increased number of field measurements, and variation in experimental outcomes due to exposure variability becomes less significant with increased number of experimental replications. We conclude that, in order for experimental findings to reflect reality, it is crucially important that exposures be performed by commercially available mobile phone handsets.

## 1. Introduction

Determination of realistic exposures from mobile phones and other wireless devices of modern telecommunications remains an important scientific challenge, especially since it is key to defining public health protection. The situation is further complicated by divergent results reported in the related literature that very well could be due to unrealistic exposure conditions, which in turn lead to ineffective and misdirected interventions.

The International Agency for Research on Cancer (IARC), while still classifying Radio Frequency (RF) Electromagnetic Fields (EMFs) as possibly carcinogenic, criticized and excluded from consideration experimental studies that used commercially available mobile phone handsets in exposing biological samples, as having “unreliable dosimetry” [1],

without further scientific rationale. Similarly the Health Protection Agency (HPA) criticized this exposure methodology reporting that the exposure is “highly variable” with “lack of control” due to network reasons (number of subscribers each moment) and movement of the animals within the vials/boxes in case of freely moving animals but recognizes that restriction of the animals during the exposures will result in additional stress. Their critique recommended that exposures should be performed by devices or handsets set to produce emissions at fixed frequency and output power by use of engineering or hardware controls [2]. In both reports the criticisms were based on the fact that real mobile phone emissions always include significant variations in their intensity, frequency, and other parameters, especially in the near-field of the antenna.

But billions of mobile phone users are daily exposed for increasing periods to real emissions from their handsets in the near-field of the antenna in contact with their ears/bodies, not to any simulated emissions with fixed parameters. Is it then scientifically correct to study the effects of a “highly variable” field by using fields with fixed parameters? In our opinion, it is not, especially in the case when the varying nature of the field seems to be an important reason for its increased biological activity.

The aim of the present study is to review biological and clinical experimental studies on mobile phone radiation effects which have employed exposures with real mobile phone emissions, as opposed to the mainstream studies which employ simulated mobile phone emissions produced by generators or test phones, and seek an explanation for the divergent results reported in the literature. In case that we find a significant conflict in the results between the two types of experimental exposures (real versus simulated), our aim is to attempt giving an explanation based on the differences between the two types of EMF-emissions.

We note that the issue of the present study applies also for every other type of RF/microwave emitting devices used in modern telecommunications, such as Internet connection wireless devices and local wireless networks (Wi-Fi), domestic cordless phones (DECT, Digitally Enhanced Cordless Technology), and baby monitors. The emissions from all these devices, although differing in specific frequencies and modulation types, are very similar. The reason that we concentrate on studies with mobile phone radiation (either real or simulated) is only the fact that they constitute the vast majority of the published studies testing the biological activity of RF/microwave EMFs.

## 2. Adaptation of Living Organisms to EMFs

Living organisms have been constantly exposed throughout evolution to terrestrial static electric and magnetic fields of average intensities  $\sim 130$  V/m and  $\sim 0.5$  G, respectively. While no adverse health effects are connected with usual exposure to these natural ambient fields, variations in their intensities on the order of 20% during “magnetic storms” or “geomagnetic pulsations” due to changes in solar activity with an average periodicity of about 11 years are connected with increased rates of animal/human health incidents, including nervous and psychic diseases, hypertensive crises, heart attacks, cerebral accidents, and mortality [3, 4].

It is clear that living organisms perceive EMFs as environmental stressors [4–7]. But since man-made EMFs constitute a very new stressor for living organisms within the billions of years of biological evolution, the cells have not developed defensive mechanisms, for example, special genes to be activated for protection against electromagnetic stress of man-made EMFs. This can be the reason why in response to man-made EMFs cells are found to activate heat-shock genes and produce heat-shock proteins very rapidly (within minutes) and at a much higher rate than for heat itself [6]. It seems to be for the same reason that mobile phone radiation is found to induce DNA damage and cell death in insect reproductive cells at a higher degree than other types of

external stressors examined before like food deprivation or chemicals [8–10]. Thus it appears that cells are much more sensitive to man-made EMFs than to other types of stress previously experienced by living organisms such as heat, cold, starvation, or chemicals. But repetitive stress leading to continuous expression of heat-shock genes or DNA damage may lead to cancer [1, 11].

One reason for the increased biological activity of man-made EMFs can be that cells/organisms adapt more easily to any external stressor, and to EMFs, when this stressor is not of significantly varying type, in other words when its parameters are kept constant or vary only slightly. Since living organisms do not have defense mechanisms against variations on the order of 20% of natural EMFs as explained above, it is realistic to expect that they do not have innate defenses against unnatural (man-made) EMFs, which are mostly not static but varying (alternating, pulsed, modulated fields, including simultaneously several different frequencies, etc.) and totally polarized in contrast to natural EMFs. [We note that even though the polarities and intensities of the static terrestrial electric and magnetic fields do not change significantly (except during specific periods as explained) there are always small changes and local variations in the direction of the field lines that make these natural static fields only partially and never totally polarized [3, 4]. This is in contrast to all man-made EMFs which are totally and invariantly polarized due to the invariant geometry of their electric circuits.]

Indeed, pulsed or modulated electromagnetic signals (radiation) are found in numerous studies published since the midseventies to be more bioactive than continuous signals of identical other parameters (intensity, frequency, duration, waveform, etc.) [12–24]. Moreover, intermittent exposure to mobile phone radiation (real or simulated) with short intermittence durations (which makes the field even more variable) is repeatedly found to be more bioactive than the corresponding continuous exposure [25, 26]. This experimental evidence further supports the argument that the more complicated and variable the field/stressor is, the more difficult it is for a living organism to adapt to it.

## 3. The Increased Variability of EMFs Emitted by Mobile Telephony Antennas

All types of digital mobile telephony radiation, except for their RF carrier signal, employ Extremely Low Frequencies (ELF) necessary for the modulation and for increasing the capacity of transmitted information by pulsing the signal. The combination of the RF carrier and the ELF pulsing frequencies has been found to be more bioactive than the RF carrier alone [16, 21]. Moreover, according to a plausible suggested mechanism [27], (a) the ELF frequencies included in any pulsed or modulated RF signal are more responsible for the biological effects, (b) changes in field intensity play a major role, and (c) the pulsing of the signal makes it twice more bioactive. A constant carrier RF wave modulated by a constant ELF field can certainly be simulated but this is not the case in real mobile telephony signals, in which both the carrier and the modulation are constantly and

unpredictably varying in intensity, frequency, and waveform during a phone-conversation [7, 28–30].

The intensity of radiation varies significantly each moment during a usual phone-conversation depending on signal reception, number of subscribers sharing the frequency band each moment, air conductivity, location within the wireless infrastructure, presence of objects and metallic surfaces, “speaking” versus “nonspeaking” mode, and so forth. These variations are much larger than 20% of the average signal intensity (as opposed to the periodical variations in the terrestrial fields known to cause health effects). Moreover the phase of the carrier signal varies continuously during a phone-conversation, and the RF frequency constantly changes between different available frequency channels, especially in third generation (3G) radiation. The wave shape is also constantly changing depending on how the changing information transmitted each moment modulates the carrier wave. Thus, the parameters of this radiation change constantly and unpredictably each moment and large, sudden, unpredictable variations in the emitted EMF/radiation take place constantly during a usual phone-conversation. The more the amount of carried information is increased (by adding text, speech, pictures, music, video, internet, etc.) in more recent phone generations (G)/types (2G, 3G, 4G, etc.), the more complicated and unpredictably varying the cell phone signals become [2, 7, 28–30].

Thus, real digital mobile phone (and other wireless communication devices) emissions change constantly and unpredictably. As a consequence, living organisms cannot adapt to such a highly varying type of stress. Moreover, due to the unpredictably varying type of the real emissions, it is impossible to simulate them by EMFs of fixed parameters.

#### 4. Real Exposure Studies as Opposed to Studies with Simulated Exposures

A significant number of studies have already been published which employed commercially available mobile phones during connection (“talk”, “listen”, or “call” modes) for exposure to a wide variety of animals (including humans)/biological samples, including *Drosophila* [6, 8, 26, 31–37], ants [38], chicken eggs [39], quails [40], human sperm *in vitro* [41, 42], human volunteers *in vivo* [43–52], mice or rats or guinea-pigs or rabbits *in vivo* [53–69], mouse cells *in vitro* [70], bees [71–73], protozoa [74], and even purified proteins *in vitro* [75]. An impressive percentage (95.8%) of these studies (46 out of 48 studies with real-life exposures) have recorded significant adverse biological or clinical effects, ranging from loss of orientation, kinetic changes, and behavioral or electroencephalographic (EEG) changes to decrease in male and female reproductive capacity, reproductive declines, molecular changes, changes in enzymatic activity, DNA damage and cell death, and histopathological changes in the brain. It was found that during “talk” mode (voice modulation) the exposure is significantly more bioactive than during “listen” mode due to the voice modulation and associated increased intensity of the emissions [7, 31]. From the remaining two studies, one reported no effect [55] and one reported an

increase in short-term memory of children [47] which we do not count as an adverse effect although it may be.

On the contrary, more than 50% of the studies performed with simulated signals have showed no effects [1, 2, 76], even though several recent review studies suggest an overall predominance of studies showing effects regardless of real or simulated exposures [7, 77–80]. A recent meta-analysis of 88 studies published during 1990–2011 investigating genetic damage in human cells from RF radiation, 87 of which did not employ real telecommunication EMFs, reported no overall association with genotoxicity [81].

Although we may have missed a few more studies with real mobile phone exposures, it becomes evident that there is a strong conflict between the overall results of studies performed with real mobile phone emissions and the overall results of studies with simulated emissions from generators and “test” phones. Moreover, while within the group of studies with simulated emissions there is also a conflict between studies that find effects and studies that do not, the group of studies with real exposures demonstrates an impressive consistency in showing effects almost at 100%. Moreover, this impressive consistency is corroborated by increasing epidemiological evidence, especially during the last years, for an association between (real-life) mobile phone use and brain tumors [82–84], by statistical studies reporting symptoms of unwellness among people residing around mobile telephony base station antennas or among mobile phone users [85–90], and by open field studies reporting declines in bird and amphibian populations around mobile telephony base station antennas [91–95].

This apparent consistency of results in the laboratory studies with real emissions and their additional corroboration with recent epidemiological/statistical and open field studies’ evidence seems to be unnoticed by health agencies and public health authorities which simply disregard these studies despite their important findings which imply the urgent establishment of much more stringent exposure limits than the current ones [96].

Although in most studies employing real mobile phone emissions the biological samples were exposed in close proximity (within the near-field up to approximately 5 cm) with the mobile phone handset, in several studies the samples/animals were exposed at greater distances in the far-field up to 1 m [32, 34, 35, 39, 51, 53, 56–58] where the intensity variations are much smaller and the dosimetry is absolutely “reliable” as is generally accepted for far-field antenna measurements [97]. In one of these studies it was found that at 20–30 cm distance from the mobile phone the biological effect (DNA damage) was even more intense than at zero distance [32].

A mobile phone antenna’s near-field extends to a distance of 5.2 or 2.6 cm, for 900 or 1800 MHz, respectively (most commonly employed carrier frequencies in 2G mobile telephony radiation), according to the relation  $r = \lambda/2\pi$ , ( $r$  is the distance of near-field far limit from the antenna when the length of the antenna is smaller than the wavelength  $\lambda$  of the emitted radiation) [98].

In studies with real mobile phone emissions investigating the dependence of observed effects on dose (radiation

intensity and/or exposure duration) [8, 31–35, 39, 40, 62], the effects have been found to be dose dependent. The dependence on dose was in most cases nonlinear, although in two studies the dependence of certain effects on exposure duration was approximating linearity [35, 62].

The results of experiments with real-life (variable) mobile phone EMFs are indeed not identically reproducible, since between successive exposures at any specific location the exact characteristics of the emitted signal are always different. But the average field values over a few minutes' (or more) period are close to each other, and thus the results of different replicate experiments with real emissions as the independent variable, although not identical quantitatively, are qualitatively similar. Statistical significance in the results can be increased by increasing the number of experimental replications while keeping rigorous control of all other parameters (animal/sample conditions, temperature, humidity, light, stray EMFs within the lab, etc.). Then, as the number of replications increases, field variability becomes less significant [99].

## 5. Discussion

In the present study we showed that the percentages of positive results differ significantly between studies with real mobile phone exposures and studies with simulated exposures, regardless of biological samples or other procedure details. The basic difference between real and simulated mobile telephony EMFs is the inherent significant variability of the first which we believe is the reason for the strong divergence in the experimental results.

In spite of the criticism on the studies employing real exposures by health agencies [1, 2] (the different aspects of which we extensively addressed) and the consequent difficulty in the publication process, the number of studies with real mobile phone emissions is increasing rapidly in the peer-reviewed literature, especially during the last years. An increasing number of scientists realize that real exposures by commercially available mobile phone handsets are the only way to represent conditions experienced by users in real-life, since they are very different and considerably more bioactive than the exposures made by simulated fields.

Any variability in the field and correspondingly in the dosimetry does not change the fact that people are actually exposed daily for increasing periods to this "highly variable" field in contact with their heads/bodies and at different distances. The presented scientific data show that this constant variation in the field makes it considerably more active biologically.

In order to have a measure of this variability, RF and ELF measurements of average intensity  $\pm$  standard deviation (SD) of the emitted real EMFs should be included in the studies, in addition to the Specific Absorption Rate (SAR) information supplied by the manufacturer (referring to a simulated human head [100]). With increasing number of measurements the SD decreases enough for the dosimetry to be judged as reliable [8, 26, 31–36, 99].

If we accepted that the real EMFs emitted by commercially available mobile phones are so much variable and their

dosimetry is so much unreliable that the studies employing real EMF-emissions are not to be taken into account because of "unknown" dosimetry, then these devices should not be approved by the public authorities to be available in the market, since unpredictable unmeasurable signal changes can result in unpredictable biological alterations. Once these devices are approved for the market (a fact that we do not challenge) the definition of the exposure is the *exposure to a user's head during a usual phone-conversation*, and this, in our opinion, should be enough for the studies to be taken into account by health agencies and authorities. Nevertheless, the measurements of the emitted EMFs suggested above are important to better quantify real-life exposures, in addition to verifying that the average emissions by the handsets used in the experiments do not transcend the existing limits [96].

It is useful to create simulations in order to study in the lab conditions of specific environments which are not accessible for laboratory work (outer space, underwater high depths, etc.). The simulations in such cases should be as close as possible to the real conditions. However, using nonrealistic simulations, especially when real conditions are easily accessible to be studied in the lab with well-controlled other parameters, is, in our opinion, a serious scientific flaw that is pervading the mobile phone bioeffects literature. The employment of simplified nonrealistic simulations may be useful for specific purposes, for example, to study what the effects would be if the signal characteristics were different, in order to improve them.

Experiments comparing the biological activity between real and simulated mobile telephony EMFs with similar average parameter values should urgently be conducted in order to test the validity of our presented arguments. Studies performed with simulated fields/exposures, especially those that did not show any effects, should, in our opinion, be repeated with real exposures of similar average signal parameters while keeping all the remaining experimental variables identical. In case that these experiments verify our arguments, health agencies should immediately revise their guidelines in regard to which studies should be considered most important and on whether the available data are indeed conflicting or not. Moreover, according to the precautionary principle, the existing exposure criteria should drastically be revised, since the effects reported in all studies with real mobile phone emissions have been recorded with EMF-intensities well below (up to thousands of times below) the existing exposure limits [8, 26, 31–75, 96].

Without account for real exposure parameters, studies suffer from imprecision that likely biases results toward null hypotheses, increasing the probability that true health risks among consumers are being missed. Simulated signals with fixed parameters bear little, if any, resemblance to what mobile phone users actually experience, even when they employ combinations of simulated signals [101–103].

In order for the biological/clinical studies testing the bioactivity of mobile telephony radiation to account for real conditions, we conclude that exposures should be performed by real EMFs as these are emitted by commercially available mobile phones. The same holds for experiments with other types of EMFs employed in modern telecommunication



systems such as DECT phones and Wi-Fi. In addition to that, simulated emissions may be used to study, for example, the effects of separate parameters of the real EMFs, but in no way should simulated emissions substitute the real ones.

As the scientific database regarding the biological effects of EMFs emitted by modern telecommunications continues to grow, it is important for experimental study designs to grow in rigor and provide a more informed basis for interpretation. One important step is to employ real-life exposures.

To investigate the biological/health effects from a widely accessible device exposing daily billions of humans we should not try to simulate the device but simply use the device itself. In particular, we should not try to simulate its real varying emissions with totally unrealistic invariant ones. This is a serious scientific flaw that may lead to totally devious results with enormous adverse consequences for public health.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Acknowledgments

The study was supported by Karolinska Institute, Stockholm, Sweden, the Irish Doctors Environmental Association, and the Alliance for Irish Radiation Protection. Professor Johansson wishes to thank Einar Rasmussen, Norway, and Brian Stein, UK, for their general support.

## References

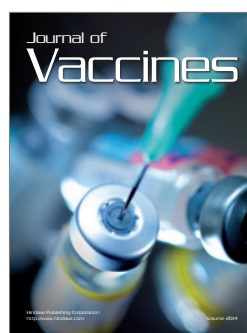
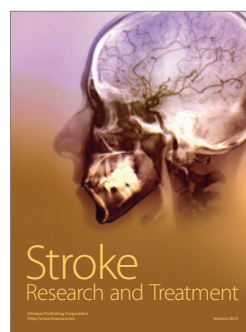
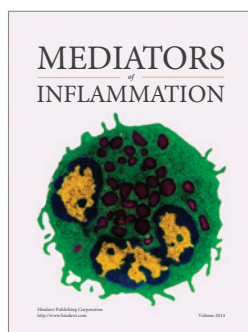
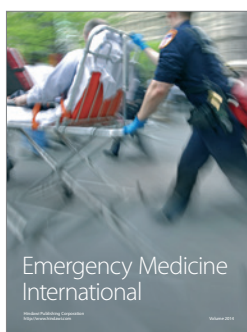
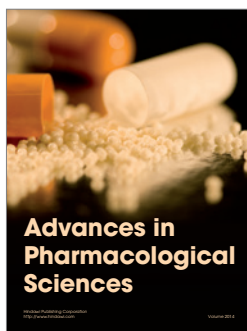
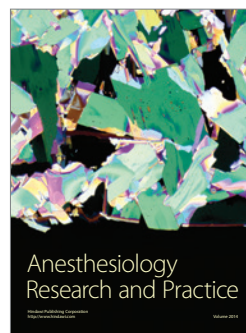
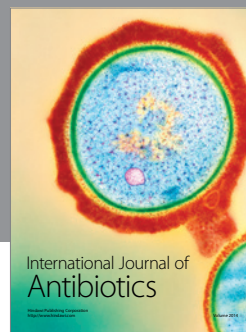
- [1] IARC, *Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields*, vol. 102, World Health Organization, 2013.
- [2] Health Protection Agency, *Health Effects from Radiofrequency Electromagnetic Fields*, 2012.
- [3] A. P. Dubrov, *The Geomagnetic Field and Life*, Plenum Press, New York, NY, USA, 1978.
- [4] A. S. Presman, *Electromagnetic Fields and Life*, Plenum Press, New York, NY, USA, 1977.
- [5] E. M. Goodman, B. Greenebaum, and M. T. Marron, "Effects of electromagnetic fields on molecules and cells," *International Review of Cytology*, vol. 158, pp. 279–338, 1995.
- [6] D. Weisbrot, H. Lin, L. Ye, M. Blank, and R. Goodman, "Effects of mobile phone radiation on reproduction and development in *Drosophila melanogaster*," *Journal of Cellular Biochemistry*, vol. 89, no. 1, pp. 48–55, 2003.
- [7] D. J. Panagopoulos, "Biological impacts, action mechanisms, dosimetry and protection issues of mobile telephony radiation," in *Mobile Phones: Technology, Networks and User Issues*, M. C. Barnes and N. P. Meyers, Eds., Nova Science Publishers, New York, NY, USA, 2011.
- [8] D. J. Panagopoulos, E. D. Chavdoula, I. P. Nezis, and L. H. Margaritis, "Cell death induced by GSM 900-MHz and DCS 1800-MHz mobile telephony radiation," *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, vol. 626, no. 1-2, pp. 69–78, 2007.
- [9] D. Drummond-Barbosa and A. C. Spradling, "Stem cells and their progeny respond to nutritional changes during *Drosophila* oogenesis," *Developmental Biology*, vol. 231, no. 1, pp. 265–278, 2001.
- [10] I. P. Nezis, D. J. Stravopodis, I. Papassideri, M. Robert-Nicoud, and L. H. Margaritis, "Stage-specific apoptotic patterns during *Drosophila* oogenesis," *European Journal of Cell Biology*, vol. 79, no. 9, pp. 610–620, 2000.
- [11] P. W. French, R. Penny, J. A. Laurence, and D. R. McKenzie, "Mobile phones, heat shock proteins and cancer," *Differentiation*, vol. 67, no. 4-5, pp. 93–97, 2001.
- [12] S. M. Bawin, L. K. Kaczmarek, and W. R. Adey, "Effects of modulated VMF fields, on the central nervous system," *Annals of the New York Academy of Sciences*, vol. 247, pp. 74–81, 1974.
- [13] S. M. Bawin and W. R. Adey, "Sensitivity of calcium binding in cerebral tissue to weak environmental electric fields oscillating at low frequency," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 73, no. 6, pp. 1999–2003, 1976.
- [14] S. M. Bawin, W. R. Adey, and I. M. Sabbot, "Ionic factors in release of  $^{45}\text{Ca}^{2+}$  from chicken cerebral tissue by electromagnetic fields," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 75, no. 12, pp. 6314–6318, 1978.
- [15] C. F. Blackman, S. G. Benane, J. A. Elder, D. E. House, J. A. Lampe, and J. M. Faulk, "Induction of calcium-ion efflux from brain tissue by radiofrequency radiation: effect of sample number and modulation frequency on the power-density window," *Bioelectromagnetics*, vol. 1, no. 1, pp. 35–43, 1980.
- [16] S. Lin-Liu and W. R. Adey, "Low frequency amplitude modulated microwave fields change calcium efflux rates from synaptosomes," *Bioelectromagnetics*, vol. 3, no. 3, pp. 309–322, 1982.
- [17] Z. Somosy, G. Thuroczy, T. Kubasova, J. Kovacs, and L. D. Szabo, "Effects of modulated and continuous microwave irradiation on the morphology and cell surface negative charge of 3T3 fibroblasts," *Scanning Microscopy*, vol. 5, no. 4, pp. 1145–1155, 1991.
- [18] B. Veyret, C. Bouthet, P. Deschaux et al., "Antibody responses of mice exposed to low-power microwaves under combined, pulse-and-amplitude modulation," *Bioelectromagnetics*, vol. 12, no. 1, pp. 47–56, 1991.
- [19] M. A. Bolshakov and S. I. Alekseev, "Bursting responses of *Lymnea* neurons to microwave radiation," *Bioelectromagnetics*, vol. 13, no. 2, pp. 119–129, 1992.
- [20] G. Thuroczy, G. Kubinyi, M. Bodo, J. Bakos, and L. D. Szabo, "Simultaneous response of brain electrical activity (EEG) and cerebral circulation (REG) to microwave exposure in rats," *Reviews on Environmental Health*, vol. 10, no. 2, pp. 135–148, 1994.
- [21] L. M. Penafiel, T. Litovitz, D. Krause, A. Desta, and J. M. Mullins, "Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells," *Bioelectromagnetics*, vol. 18, no. 2, pp. 132–141, 1997.
- [22] A. Höytö, J. Luukkonen, J. Juutilainen, and J. Naarala, "Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants," *Radiation Research*, vol. 170, no. 2, pp. 235–243, 2008.
- [23] S. Franzellitti, P. Valbonesi, N. Ciancaglini et al., "Transient DNA damage induced by high-frequency electromagnetic fields (GSM 1.8 GHz) in the human trophoblast HTR-8/SVneo cell line evaluated with the alkaline comet assay," *Mutation Research—Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 683, no. 1-2, pp. 35–42, 2010.

- [24] A. Campisi, M. Gulino, R. Acquaviva et al., "Reactive oxygen species levels and DNA fragmentation on astrocytes in primary culture after acute exposure to low intensity microwave electromagnetic field," *Neuroscience Letters*, vol. 473, no. 1, pp. 52–55, 2010.
- [25] E. Diem, C. Schwarz, F. Adlkofer, O. Jahn, and H. Rüdiger, "Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro," *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, vol. 583, no. 2, pp. 178–183, 2005.
- [26] E. D. Chavdoula, D. J. Panagopoulos, and L. H. Margaritis, "Comparison of biological effects between continuous and intermittent exposure to GSM-900 MHz mobile phone radiation: detection of apoptotic cell-death features," *Mutation Research*, vol. 700, no. 1-2, pp. 51–61, 2010.
- [27] D. J. Panagopoulos, A. Karabarounis, and L. H. Margaritis, "Mechanism for action of electromagnetic fields on cells," *Biochemical and Biophysical Research Communications*, vol. 298, no. 1, pp. 95–102, 2002.
- [28] J. Tisal, *GSM Cellular Radio Telephony*, John Wiley & Sons, West Sussex, UK, 1998.
- [29] F. Hillebrand, *GMS and UMTS. The Creation of Global Mobile Communication*, John Wiley & Sons, Chichester, UK, 2002.
- [30] P. Curwen and J. Whalley, "Mobile communications in the 21st century," in *Mobile Telephones: Networks, Applications and Performance*, A. C. Harper and R. V. Bures, Eds., pp. 29–75, Nova Science Publishers, 2008.
- [31] D. J. Panagopoulos, A. Karabarounis, and L. H. Margaritis, "Effect of GSM 900-MHz mobile phone radiation on the reproductive capacity of *Drosophila melanogaster*," *Electromagnetic Biology and Medicine*, vol. 23, no. 1, pp. 29–43, 2004.
- [32] D. J. Panagopoulos, E. D. Chavdoula, and L. H. Margaritis, "Bioeffects of mobile telephony radiation in relation to its intensity or distance from the antenna," *International Journal of Radiation Biology*, vol. 86, no. 5, pp. 345–357, 2010.
- [33] D. J. Panagopoulos, E. D. Chavdoula, A. Karabarounis, and L. H. Margaritis, "Comparison of bioactivity between GSM 900 MHz and DCS 1800 MHz mobile telephony radiation," *Electromagnetic Biology and Medicine*, vol. 26, no. 1, pp. 33–44, 2007.
- [34] D. J. Panagopoulos and L. H. Margaritis, "The identification of an intensity 'window' on the bioeffects of mobile telephony radiation," *International Journal of Radiation Biology*, vol. 86, no. 5, pp. 358–366, 2010.
- [35] D. J. Panagopoulos and L. H. Margaritis, "The effect of exposure duration on the biological activity of mobile telephony radiation," *Mutation Research*, vol. 699, no. 1-2, pp. 17–22, 2010.
- [36] D. J. Panagopoulos, "Effect of microwave exposure on the ovarian development of *Drosophila melanogaster*," *Cell Biochemistry and Biophysics*, vol. 63, no. 2, pp. 121–132, 2012.
- [37] L. H. Margaritis, A. K. Manta, K. D. Kokkaliaris et al., "*Drosophila oogenesis* as a bio-marker responding to EMF sources," *Electromagnetic Biology and Medicine*, vol. 33, no. 3, pp. 165–189, 2014.
- [38] M.-C. Cammaerts and O. Johansson, "Ants can be used as bio-indicators to reveal biological effects of electromagnetic waves from some wireless apparatus," *Electromagnetic Biology and Medicine*, vol. 33, no. 4, pp. 282–288, 2014.
- [39] F. Batellier, I. Couty, D. Picard, and J. P. Brillard, "Effects of exposing chicken eggs to a cell phone in 'call' position over the entire incubation period," *Theriogenology*, vol. 69, no. 6, pp. 737–745, 2008.
- [40] O. Tsybulin, E. Sidorik, O. Brieieva et al., "GSM 900 MHz cellular phone radiation can either stimulate or depress early embryogenesis in Japanese quails depending on the duration of exposure," *International Journal of Radiation Biology*, vol. 89, no. 9, pp. 756–763, 2013.
- [41] A. Agarwal, N. R. Desai, K. Makker et al., "Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study," *Fertility and Sterility*, vol. 92, no. 4, pp. 1318–1325, 2009.
- [42] I. Gorpichenko, O. Nikitin, O. Banyra, and A. Shulyak, "The influence of direct mobile phone radiation on sperm quality," *Central European Journal of Urology*, vol. 67, no. 1, pp. 65–71, 2014.
- [43] A. S. Yadav and M. K. Sharma, "Increased frequency of micronucleated exfoliated cells among humans exposed in vivo to mobile telephone radiations," *Mutation Research—Genetic Toxicology and Environmental Mutagenesis*, vol. 650, no. 2, pp. 175–180, 2008.
- [44] S. T. Çam and N. Seyhan, "Single-strand DNA breaks in human hair root cells exposed to mobile phone radiation," *International Journal of Radiation Biology*, vol. 88, no. 5, pp. 420–424, 2012.
- [45] Q. Luo, Y. Jiang, M. Jin, J. Xu, and H.-F. Huang, "Proteomic analysis on the alteration of protein expression in the early-stage placental villous tissue of electromagnetic fields associated with cell phone exposure," *Reproductive Sciences*, vol. 20, no. 9, pp. 1055–1061, 2013.
- [46] M. Mandalà, V. Colletti, L. Sacchetto et al., "Effect of bluetooth headset and mobile phone electromagnetic fields on the human auditory nerve," *Laryngoscope*, vol. 124, no. 1, pp. 255–259, 2014.
- [47] M. M. Movvahedi, A. Tavakkoli-Golpayegani, S. A. Mortazavi et al., "Does exposure to GSM 900 MHz mobile phone radiation affect short-term memory of elementary school students?" *Journal of Pediatric Neurosciences*, vol. 9, no. 2, pp. 121–124, 2014.
- [48] H. D'Costa, G. Trueman, L. Tang et al., "Human brain wave activity during exposure to radiofrequency field emissions from mobile phones," *Australasian Physical and Engineering Sciences in Medicine*, vol. 26, no. 4, pp. 162–167, 2003.
- [49] F. Ferreri, G. Curcio, P. Pasqualetti, L. De Gennaro, R. Fini, and P. M. Rossini, "Mobile phone emissions and human brain excitability," *Annals of Neurology*, vol. 60, no. 2, pp. 188–196, 2006.
- [50] F. Vecchio, C. Babiloni, F. Ferreri et al., "Mobile phone emission modulates interhemispheric functional coupling of EEG alpha rhythms," *European Journal of Neuroscience*, vol. 25, no. 6, pp. 1908–1913, 2007.
- [51] F. Vecchio, C. Babiloni, F. Ferreri et al., "Mobile phone emission modulates inter-hemispheric functional coupling of EEG alpha rhythms in elderly compared to young subjects," *Clinical Neurophysiology*, vol. 121, no. 2, pp. 163–171, 2010.
- [52] F. Vecchio, M. Tombini, P. Buffo et al., "Mobile phone emission increases inter-hemispheric functional coupling of electroencephalographic  $\alpha$  rhythms in epileptic patients," *International Journal of Psychophysiology*, vol. 84, no. 2, pp. 164–171, 2012.
- [53] A. İlhan, A. Gurel, F. Armutcu et al., "Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain," *Clinica Chimica Acta*, vol. 340, no. 1-2, pp. 153–162, 2004.
- [54] M. A. Elhag, G. M. Nabil, and A. M. Attia, "Effects of electromagnetic field produced by mobile phones on the oxidant and antioxidant status of rats," *Pakistan Journal of Biological Sciences*, vol. 10, no. 23, pp. 4271–4274, 2007.

- [55] S. Dasdag, M. Z. Akdag, F. Aksen et al., "Whole body exposure of rats to microwaves emitted from a cell phone does not affect the testes," *Bioelectromagnetics*, vol. 24, no. 3, pp. 182–188, 2003.
- [56] A. R. Ferreira, T. Knakievicz, M. A. de Bittencourt Pasquali et al., "Ultra high frequency-electromagnetic field irradiation during pregnancy leads to an increase in erythrocytes micronuclei incidence in rat offspring," *Life Sciences*, vol. 80, no. 1, pp. 43–50, 2006.
- [57] J.-G. Yan, M. Agresti, T. Bruce, Y. H. Yan, A. Granlund, and H. S. Matloub, "Effects of cellular phone emissions on sperm motility in rats," *Fertility and Sterility*, vol. 88, no. 4, pp. 957–964, 2007.
- [58] M. Balci, E. Devrim, and I. Durak, "Effects of mobile phones on oxidant/antioxidant balance in cornea and lens of rats," *Current Eye Research*, vol. 32, no. 1, pp. 21–25, 2007.
- [59] M. Mailankot, A. P. Kunnath, H. Jayalekshmi, B. Koduru, and R. Valsalan, "Radio frequency electromagnetic radiation (RF-EMR) from GSM (0.9/1.8GHZ) mobile phones induces oxidative stress and reduces sperm motility in rats," *Clinics*, vol. 64, no. 6, pp. 561–565, 2009.
- [60] A. Gul, H. Çelebi, and S. Uğraş, "The effects of microwave emitted by cellular phones on ovarian follicles in rats," *Archives of Gynecology and Obstetrics*, vol. 280, no. 5, pp. 729–733, 2009.
- [61] E. B. Imge, B. Kilicoğlu, E. Devrim, R. Çetin, and I. Durak, "Effects of mobile phone use on brain tissue from the rat and a possible protective role of vitamin C—a preliminary study," *International Journal of Radiation Biology*, vol. 86, no. 12, pp. 1044–1049, 2010.
- [62] T. S. Aldad, G. Gan, X.-B. Gao, and H. S. Taylor, "Fetal radiofrequency radiation exposure from 800–1900 mhz-rated cellular telephones affects neurodevelopment and behavior in mice," *Scientific Reports*, vol. 2, article 312, 2012, Erratum in: *Scientific Reports*, vol. 3, article 1320, 2013.
- [63] M. A. Al-Damegh, "Rat testicular impairment induced by electromagnetic radiation from a conventional cellular telephone and the protective effects of the antioxidants vitamins C and E," *Clinics*, vol. 67, no. 7, pp. 785–792, 2012.
- [64] O. Koca, A. M. Gökçe, M. I. Öztürk, F. Ercan, N. Yurdakul, and M. I. Karaman, "Effects of intensive cell phone (Philips Genic 900) use on the rat kidney tissue," *Urology Journal*, vol. 10, no. 2, pp. 886–891, 2013.
- [65] S. A. Meo and K. A. Rubaan, "Effects of exposure to electromagnetic field radiation (EMFR) generated by activated mobile phones on fasting blood glucose," *International Journal of Occupational Medicine and Environmental Health*, vol. 26, no. 2, pp. 235–241, 2013.
- [66] T. K. Motawi, H. A. Darwish, Y. M. Moustafa, and M. M. Labib, "Biochemical modifications and neuronal damage in brain of young and adult rats after long-term exposure to mobile phone radiations," *Cell Biochemistry and Biophysics*, vol. 70, no. 2, pp. 845–855, 2014.
- [67] I. Meral, H. Mert, N. Mert et al., "Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs," *Brain Research*, vol. 1169, no. 1, pp. 120–124, 2007.
- [68] I. Meral, Y. Tekintangac, and H. Demir, "Effects of 900 MHz electromagnetic field emitted by cellular phones on electrocardiograms of guinea pigs," *Human and Experimental Toxicology*, vol. 33, no. 2, pp. 164–169, 2014.
- [69] M. K. Irmak, E. Fadilloğlu, M. Güleç, H. Erdoğan, M. Yağmurca, and Ö. Akyol, "Effects of electromagnetic radiation from a cellular telephone on the oxidant and antioxidant levels in rabbits," *Cell Biochemistry and Function*, vol. 20, no. 4, pp. 279–283, 2002.
- [70] C. Liu, P. Gao, S.-C. Xu et al., "Mobile phone radiation induces mode-dependent DNA damage in a mouse spermatocyte-derived cell line: a protective role of melatonin," *International Journal of Radiation Biology*, vol. 89, no. 11, pp. 993–1001, 2013.
- [71] V. P. Sharma and N. R. Kumar, "Changes in honeybee behaviour and biology under the influence of cellphone radiations," *Current Science*, vol. 98, no. 10, pp. 1376–1378, 2010.
- [72] N. R. Kumar, S. Sangwan, and P. Badotra, "Exposure to cell phone radiations produces biochemical changes in worker honey bees," *Toxicology International*, vol. 18, no. 1, pp. 70–72, 2011.
- [73] D. Favre, "Mobile phone-induced honeybee worker piping," *Apidologie*, vol. 42, no. 3, pp. 270–279, 2011.
- [74] M.-C. Cammaerts, O. Debeir, and R. Cammaerts, "Changes in *Paramecium caudatum* (Protozoa) near a switched-on GSM telephone," *Electromagnetic Biology and Medicine*, vol. 30, no. 1, pp. 57–66, 2011.
- [75] M. Barteri, A. Pala, and S. Rotella, "Structural and kinetic effects of mobile phone microwaves on acetylcholinesterase activity," *Biophysical Chemistry*, vol. 113, no. 3, pp. 245–253, 2005.
- [76] L. Verschaeve, J. Juutilainen, I. Lagroye et al., "In vitro and in vivo genotoxicity of radiofrequency fields," *Mutation Research/Reviews in Mutation Research*, vol. 705, no. 3, pp. 252–268, 2010.
- [77] L. Verschaeve, "Genetic damage in subjects exposed to radiofrequency radiation," *Mutation Research*, vol. 681, no. 2-3, pp. 259–270, 2009.
- [78] S. La Vignera, R. A. Condorelli, E. Vicari, R. D'Agata, and A. E. Calogero, "Effects of the exposure to mobile phones on male reproduction: a review of the literature," *Journal of Andrology*, vol. 33, no. 3, pp. 350–356, 2012.
- [79] S. Cucurachi, W. L. M. Tãmis, M. G. Vijver, W. J. G. M. Peijnenburg, J. F. B. Bolte, and G. R. de Snoo, "A review of the ecological effects of radiofrequency electromagnetic fields (RF-EMF)," *Environment International*, vol. 51, pp. 116–140, 2013.
- [80] A. Balmori, "Electrosmog and species conservation," *Science of the Total Environment*, vol. 496, pp. 314–316, 2014.
- [81] P. T. J. Vijayalaxmi, "Genetic damage in human cells exposed to non-ionizing radiofrequency fields: a meta-analysis of the data from 88 publications (1990–2011)," *Mutation Research—Genetic Toxicology and Environmental Mutagenesis*, vol. 749, no. 1-2, pp. 1–16, 2012.
- [82] M. Kundi, "Mobile phone use and cancer," *Occupational and Environmental Medicine*, vol. 61, no. 6, pp. 560–570, 2004.
- [83] V. G. Khurana, C. Teo, M. Kundi, L. Hardell, and M. Carlberg, "Cell phones and brain tumors: a review including the long-term epidemiologic data," *Surgical Neurology*, vol. 72, no. 3, pp. 205–214, 2009.
- [84] L. Hardell, M. Carlberg, F. Söderqvist, and K. H. Mild, "Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use," *International Journal of Oncology*, vol. 43, no. 6, pp. 1833–1845, 2013.
- [85] E. A. Navarro, J. Segura, M. Portolés, and C. Gómez-Perretta, "The microwave syndrome: a preliminary study in Spain," *Electromagnetic Biology and Medicine*, vol. 22, no. 2-3, pp. 161–169, 2003.
- [86] O. E. Salama and R. M. Abou El Naga, "Cellular phones: are they detrimental?" *The Journal of the Egyptian Public Health Association*, vol. 79, no. 3-4, pp. 197–223, 2004.



- [87] H.-P. Hutter, H. Moshhammer, P. Wallner, and M. Kundi, "Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations," *Occupational and Environmental Medicine*, vol. 63, no. 5, pp. 307–313, 2006.
- [88] M. Blettner, B. Schlehofer, J. Breckenkamp et al., "Mobile phone base stations and adverse health effects: phase I of a population-based, cross-sectional study in Germany," *Occupational and Environmental Medicine*, vol. 66, no. 2, pp. 118–123, 2009.
- [89] M. Kundi and H.-P. Hutter, "Mobile phone base stations—effects on wellbeing and health," *Pathophysiology*, vol. 16, no. 2–3, pp. 123–135, 2009.
- [90] J.-F. Viel, S. Clerc, C. Barrera et al., "Residential exposure to radiofrequency fields from mobile phone base stations, and broadcast transmitters: a population-based survey with personal meter," *Occupational and Environmental Medicine*, vol. 66, no. 8, pp. 550–556, 2009.
- [91] A. Balmori, "Possible effects of electromagnetic fields from phone masts on a population of white stork (*Ciconia ciconia*)," *Electromagnetic Biology and Medicine*, vol. 24, no. 2, pp. 109–119, 2005.
- [92] A. Balmori and Ö. Hallberg, "The urban decline of the house sparrow (*Passer domesticus*): A possible link with electromagnetic radiation," *Electromagnetic Biology and Medicine*, vol. 26, no. 2, pp. 141–151, 2007.
- [93] J. Everaert and D. Bauwens, "A possible effect of electromagnetic radiation from mobile phone base stations on the number of breeding house sparrows (*Passer domesticus*)," *Electromagnetic Biology and Medicine*, vol. 26, no. 1, pp. 63–72, 2007.
- [94] R. Bhattacharya and R. Roy, "Impact of electromagnetic pollution from mobile phone towers on local birds," *International Journal of Innovative Research in Science Engineering and Technology*, vol. 3, pp. 32–36, 2014.
- [95] A. Balmori, "Mobile phone mast effects on common frog (*Rana temporaria*) tadpoles: the city turned into a laboratory," *Electromagnetic Biology and Medicine*, vol. 29, no. 1–2, pp. 31–35, 2010.
- [96] ICNIRP, "Guidelines for limiting exposure to time-varying electric, magnetic and electromagnetic fields (up to 300GHz)," *Health Physics*, vol. 74, pp. 494–522, 1998.
- [97] D. Slater, *Near-Field Antenna Measurements*, Artech House, 1991.
- [98] WHO, *Environmental Health Criteria 137. Electromagnetic Fields 300Hz to 300GHz*, World Health Organization, Geneva, Switzerland, 1993.
- [99] J. Maber, *Data Analysis for Biomolecular Sciences*, Longman, London, UK, 1999.
- [100] O. P. Gandhi, L. L. Morgan, A. A. de Salles, Y.-Y. Han, R. B. Herberman, and D. L. Davis, "Exposure limits: the underestimation of absorbed cell phone radiation, especially in children," *Electromagnetic Biology and Medicine*, vol. 31, no. 1, pp. 34–51, 2012.
- [101] N. Kuster and F. Schönborn, "Recommended minimal requirements and development guidelines for exposure setups of bio-experiments addressing the health risk concern of wireless communications," *Bioelectromagnetics*, vol. 21, no. 7, pp. 508–514, 2000.
- [102] H. Ndoumbè Mbonjo Mbonjo, J. Streckert, A. Bitz et al., "Generic UMTS test signal for RF bioelectromagnetic studies," *Bioelectromagnetics*, vol. 25, no. 6, pp. 415–425, 2004.
- [103] J. Czyz, K. Guan, Q. Zeng et al., "High frequency electromagnetic fields (GSM signals) affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells," *Bioelectromagnetics*, vol. 25, no. 4, pp. 296–307, 2004.



Neurological; Book Chapter, A Summary of Recent Literature (2007-2017)  
on Neurological Effects of Radiofrequency Radiation,  
Prof. Lai; 2018 Referenced 122 Studies.

Lai, H. A summary of recent literature on neurobiological effects of radiofrequency radiation. in “*Mobile Communications and Public Health*” Markov, M. (ed.), CRC Press, Boca Raton, FL, 2018, Chapter 8, pp.187-222

## **A Summary of Recent Literature (2007-2017) on Neurological Effects of Radiofrequency Radiation**

**Henry Lai**  
**Department of Bioengineering,**  
**University of Washington,**  
**Seattle, WA 98195, USA**  
(hlai@u.washington.edu)

### **Introduction**

Neurological effects are caused by changes in the nervous system. Factors that act directly or indirectly on the nervous system causing morphological, chemical, or electrical changes in the nervous system can lead to neurological effects. The final manifestation of these effects can be seen as psychological/behavioral changes, e.g., memory, learning, and perception. The nervous system is an electrical organ. Thus, it should not be surprising that exposure to electromagnetic fields could lead to neurological changes. Morphological, chemical, electrical, and behavioral changes have been reported in animals and cells after exposure to nonionizing electromagnetic fields (EMF) across a range of frequencies. The consequences of physiological changes in the nervous system are very difficult to assess. We don't quite understand how the nervous system functions and reacts to external perturbations. The highly flexible nervous system could easily compensate for external disturbances. On the other hand, the consequence of neural perturbation is also situation-dependent. For example, an EMF-induced change in brain electrical activity could lead to different consequences depending on whether a person is watching TV or driving a car.

The following is a summary of the research literature on the neurological effects of exposure to radiofrequency radiation (RFR), a part of the EMF spectrum that is used in wireless communications, published between 2007- 2017. The database came from survey of the Medline and understandably does not include all the relevant papers published during the period.

### **The Studies**

There are many new studies on human subjects. Many of them are on changes in brain electrical activities after exposure to cell phone radiation. Bak et al (2010) (Global System for Mobile Communication (GSM) 935 MHz, 217 Hz pulses, 20 min, 0.0052 mW/cm<sup>2</sup>) reported effects on event-related brain potentials. Maganioti et al. (2010) (900 MHz and 1800 MHz, 45 min) further reported that RFR affected the gender-specific components of event-related

potentials (see also Hountala et al., 2008). Croft et al (2008) (GSM 895 MHz, modulated at 217 Hz, 0.11 W/kg over 10 gm tissue, 30 min) reported changes of the alpha-wave power of electroencephalogram (EEG). They (Croft et al., 2010) further reported that effects differed between 2-G and 3-G cell phone transmission systems (2-G 894.6 MHz 217-Hz modulation, 0.7 W/kg over 10 gm tissue; 1900-MHz 3-G-modulated signal, 1.7 W/kg over 10 gm tissue; 55 min) on resting alpha activity in young adults. They observed effects after exposure to 2G but not 3G cell phone radiation, whereas Leung et al. (2011) (conditions similar to Croft et al. (2010)) found similar EEG effects (delayed ERD/ERS responses of the alpha power) with both 2G and 3G radiations. However, it is difficult to compare the 2-G and 3-G exposure conditions with different SAR and energy distributions. Ghosn et al. (2015) (GSM 900 MHz, peak specific absorption rate (SAR) 0.93 W/kg, 26 min) also reported GSM EMF affected alpha band of resting human EEG. Lustenberger et al. (2013) (900 MHz RFR pulsed with 500 msec bursts, spatial peak SAR 0.15 W/kg over 10 gm tissue) found increased slow-wave activity in humans during exposure to pulse-modulated RFR toward the end of the sleep period. Vecchio and associates reported that cell phone RFR affected EEG and the spread of neural synchronization conveyed by inter-hemispherical functional coupling of EEG rhythms (Vecchio et al., 2007) (GSM signal at 902.4 MHz, 8.33 and 217 Hz modulations, peak SAR 0.5 W/kg, 45 min) and modulated event-related desynchronization of alpha rhythms and enhanced human cortical neural efficiency (Vecchio et al., 2012a) (exposure conditions same as Vecchio et al., 2007). Naziroğlu and Gümrall (2009) (2450 MHz pulsed at 217 Hz, 1.73 W/kg, 60 min/day for 28 days) reported a significant change in cortical EEG spikes in rats after chronic RFR exposure. RFR exposure modulated the spontaneous low frequency fluctuations in some brain regions (Lv et al., 2014a) (2573 MHz, spatial peak SAR 0.9 and 1.07 W/kg over 10 gm tissue, 30 min) and the synchronization patterns of EEG activation across the whole brain (Lv et al., 2014b) (exposure conditions similar to Lv et al., 2014a) in humans. An interesting finding is that RFR could interact with the activity of brain epileptic foci in epileptic patients (Tombini et al., 2013; Vecchio et al., 2012b). Roggeveen et al. (2015 a,b) (1929.1 to 1939.7 MHz, 0.69 W/kg, 15 min) reported significant changes in several bands of human EEG and detection of radiation peaks when exposed to the RFR from a 3G mobile phone. These effects were observed only when the phone was placed on the ear, and not on the heart. Yang et al. (2017) reported a reduction in spectral power in the alpha and beta bands in the frontal and temporal cortical regions of humans exposed to Long-Term Evolution (LTE) cell phone radiation. However, no significant effect on human EEG was reported by Perentos et al. (2007) (CW RFR 15 min, pulsed RFR 15 min) and Trunk et al. (2013) (1947-MHz 3G Universal Mobile Telecommunication System (UMTS), 1.75 W/kg 2 cm from surface of head model, 30 min), Trunk et al. (2014) (1947-MHz 3G UMTS signals, peak SAR 1.75 W/kg, 15 min)), and Kleinlogel et al. (2008 a, b) (1950 MHz UMTS (SAR 0.1 and 1 W/kg) and pulsed 900 MHz GSM (1 W/kg), ~30 min) also reported no significant effects on resting EEG and event-related potentials in humans after exposure to cell phone RFR. Furthermore, Krause et al. (2007) (902 MHz continuous-wave (CW) or pulsed at 217 Hz, pulse width 0.577 msec, averaged SAR 0.738 W/kg over 10 gm of tissue, peak 1.18W/kg) reported no significant effect of cell phone radiation on brain oscillatory activity, and Inomata-Terada et al. (2007) (800 MHz Time-Division Multiple Access (TDMA), 0.054 W/kg over 10 gm of tissue, 30 min) concluded that cell phone radiation does not affect the electrical activity of the motor cortex.

There are studies on the effects of cell phone radiation on EEG during sleep. Changes in sleep EEG have been reported by Hung et al. (2007) (GSM 900 MHz, SAR over 10 gm of tissue varied from  $< 0.001 - 0.133$  W/kg depending the mode the cell phone was in, during sleep), Loughran et al. (2012) (894.6 MHz pulse-modulated at 217 Hz, peak spatial SAR 0.674 W/kg over 10 gm of tissue, 30 min prior to sleep), Lowden et al (2011) (GSM 884 MHz, spatial peak SAR 1.4W/kg, 3 hr prior to sleep), Regel et al. (2007) (pulse-modulated GSM 900 MHz signal, 0.2 or 5 W/kg, 30 min prior to sleep), and Schmid et al. (2012 a,b) (900 MHz modulated at 2 Hz, 2 W/kg). No significant effect was reported by Fritzer et al (2007) (GSM 900 with 2, 8, 217, 1733 Hz modulations, peak SAR within head 1 W/kg, during sleep), Mohler et al. (2010, 2012) (no details on exposure conditions), and Nakatani-Enomoto et al. (2013) (W-Code-Division Multiple Access (CDMA)-like signal, SAR over 10 gm tissue in the head and brain 1.52 and 0.13 W/kg, respectively, 3 hr). Loughran et al. (2012) provided an interesting conclusion in their paper: “These results confirm previous findings of mobile phone-like emissions affecting the EEG during non-rapid eye movement (REM) sleep. Importantly, this low-level effect was also shown to be sensitive to individual variability. Furthermore, this indicates that “previous negative results are not strong evidence for a lack of an effect...” More recently, Lustenberger et al. (2015) (900 MHz, 2 Hz pulse, peak spatial SAR 2 W/kg over 10 gm tissue, 30 min) reported pulsed-RFR-exposure-related increases in delta-theta EEG frequency range in several fronto-central brain areas in humans during non-REM sleep. Increase in REM sleep (Pelletier et al., 2013) (CW 900 MHz, 1 V/m, 0.0001 – 0.0003 W/kg, 5 weeks) and increases in duration and frequency of slow-wave sleep (Pelletier et al., 2014) (exposure conditions same as Pelletier et al., 2013) have been reported in developing rats after chronic RFR exposure. Mohammed et al. (2013) reported a disturbance in REM sleep EEG in the rat after long term exposure (1 hr/day for 1 month) to a 900-MHz modulated RFR.

Studies on the effects of RFR on the blood-brain barrier continued. Increase in blood-brain barrier permeability in animals after exposure to RFR was first reported in the 1970s. Such change could lead to entry of toxic substances into the brain. On the other hand, the possibility of using RFR to open up the blood-brain barrier to facilitate entry of therapeutic drugs into the brain has also be explored. In the last decade, the Salford group in Sweden continued to confirm their earlier findings on blood-brain barrier permeability and cell death in the brain (Eberhardt et al., 2008, Nittby et al., 2008a, 2009). Effects were observed after a single exposure (2 hr) to RFR at low SAR (0.00012-0.12 W/kg). In the meantime, there are several studies reporting effects of RFR on the blood-brain barrier. Sirav and Seyhan (2009, 2011) reported increased blood-brain barrier permeability in the rat after a 20-min exposure to continuous-wave 900 MHz and 1800 MHz RFR. The SARs in the 2011 study were 0.00426 W/kg for 900-MHz and 0.0014 W/kg for 1800 MHz. Interestingly, effect was observed only in male and not female rats. In a more recent study, Sirav and Seyhan (2016) studied the effects of pulse-modulated (217 Hz, 557  $\mu$ s) 900-MHz and 1800-MHz RFR at 0.02 W/kg. They reported an increase in blood-brain barrier permeability in male rats after 20 min of exposure to either 900-MHz or 1800-MHz pulsed RFR, whereas an effect was found in female rats only after exposure



to the 900-MHz field. Tan et al. (2015) also reported an increase in blood-brain barrier permeability in rats after repeated exposure (14 or 28 days, 3 hr/day) to a 900 MHz field (brain SAR 2 W/kg). They suggested the involvement of the mtk-1/extracellular signal regulated kinase (ERK) for the effect. Wang LF et al. (2015), using an in vitro model, reported broadening of tight junctions in ECV304 cells and astrocytes. The authors implied the involvement of the vascular endothelial growth factor (VEGF)/Flk-1-ERK pathway in the effect. There is a related series of experiments on human subjects by Söderqvist et al. (2009 a,b,c). The authors reported a leakage of the blood-cerebrospinal fluid barrier and not the brain-brain barrier in subjects exposed to cell phone or cordless phone radiation. There are studies that reported no significant effect of RFR exposure on the blood-brain barrier. Kumlin et al. (2007) reported no neuronal cell death and significant change in the blood-brain barrier in juvenile rats after exposure to RFR (900 MHz, 0.3-3 W/kg, 2 hr/day, 5 days/week, 5 weeks). de Gannes et al. (2009) reported no significant effect on blood-brain barrier permeability and apoptosis of brain cells in rats after a 2hr-exposure to GSM 900 MHz at brain SAR of 0.14 and 20 W/kg. Finnie et al. (2009a,b) also reported no significant effects on the blood-brain barrier (based on expression of the water channel protein AQP-4 in the brain) in mice after exposure to RFR (900 MHz, 4 W/kg, 60 min or 60 min/day, 5 days/week for 104 weeks). More recently, Poullietier de Gannes et al. (2017) reported no significant changes in blood-brain barrier and neuronal degeneration in rats after a single (2 hr) or repeated (2 h/day, 5 days/week for 4 weeks) exposure to GSM-1800 and UMTS-1950 signals up to a brain-average SAR of 13 W/kg. However, an increase in albumin leakage was observed at 50 days after exposure in the brain of rats repeatedly exposed to both RF signals at 13 W/kg. Regarding “dark neurons” in the brain of rats exposed to RFR reported by Salford et al. (2003), which is apparently related to change in the blood-brain barrier. There are five reports showing an increase in dark neurons (Eberhardt et al., 2008; Kerimoğlu et al., 2016a; Köktürk et al., 2013; Jorge-Mora et al., 2013; Odaci et al., 2016), whereas de Gannes et al. (2009), Grafström et al. (2008), and Masuda et al. (2009) did not observe such an effect in the brain of RFR-exposed animals.

Related to the blood-brain barrier is a group of studies on astrocyte and microglia. These are cells in the blood-brain barrier that support the endothelial cells that form the barrier. Effects of RFR on these cells could conceivably affect the function of the blood-brain barrier. RFR-induced effects of astrocytes have been reported by Ammari et al. (2008a, 2010), Brillaud et al. (2007), Choi and Choi (2016), Liu et al. (2012), Lu et al. (2014), Maskey et al. (2010b, 2012), and Zhao et al. (2007), whereas no significant effect was reported by Bouji et al. (2012), Chen et al. (2014), Kumari et al. (2017) and Watilliaux et al. (2011). In studies on microglia, Hao et al. (2010), He et al. (2016), Lu et al. (2014) and Yang et al. (2010) reported effects of RFR exposure, whereas no significant effect was reported by Finnie et al. (2010), Hirose et al. (2010), and Watilliaux et al. (2011).

There are studies on the effects of cell phone radiation and the auditory system. Most research (Bhagat et al., 2016; Gupta et al., 2015; Kwon 2009, 2010a, b; Parazzini et al., 2009;



Stefanics et al., 2007, 2008) reported no effects, which seems to agree with the pre-2007 studies in this area. However, there are two reports by Kaprana et al. (2011) and Khullar et al. (2013) showing effects on auditory brainstem response, two papers by Panda et al. (2010, 2011) that concluded: “Long-term and intensive GSM and CDMA mobile phone use may cause damage to cochlea as well as the auditory cortex.”, and a paper (Mandalà et al., 2014) reporting effect on auditory-evoked cochlear nerve response. Maskey and Kim (2014) reported a decrease in neurotrophins that are important in the regulation of neuron survival in the superior olivary complex, a neural component of the auditory system, in mice after chronic exposure to RFR. Velayutham et al. (2014) reported hearing loss in cell phone users and Sudan et al. (2013) observed weak associations between cell phone use and hearing loss in children at age 7. These effects may not be caused by the radiation. However, there is a study (Seckin et al., 2014) showing structural damage in the cochlea of the rat after prenatal exposure to RFR. And, Ozgur et al. (2015) reported neuronal degeneration in the cochlear nucleus of the auditory system in the rat after chronic exposure to RFR. Kwon et al. (2010a) reported that short-term exposure to cell phone radiation did not significantly affect the transmission of sensory stimuli from the cochlea to the midbrain along the auditory nerve and brainstem auditory pathways, and (Kwon et al., 2010b) no significant effect on auditory sensory memory in children. More recently, Çeliker et al. (2017) also reported no significant change in auditory brainstem responses, but increases in neuronal degeneration and apoptosis in the cochlear nucleus in rats exposed to a 2100-MHz field for 30 days.

There are several studies that showed neurological changes in humans after use of wireless devices, but those changes apparently were not caused by exposure to the radiation. Abramson et al. (2009) reported changes in cognitive functions in young adolescents. (“The accuracy of working memory was poorer, reaction time for a simple learning task shorter, associative learning response time shorter and accuracy poorer in children reporting more mobile phone voice calls”). Arns et al. (2007) observed more focused attention in frequent cell phone users, which was probably a “cognitive training effect”. Yuan et al. (2011) reported morphological changes in the brain of adolescents with “internet addiction disorder”.

There are several studies showing differential effects of different waveforms. This is an important consideration in understanding how EMF interacts with living organisms. Croft et al. (2010) reported that 2G, but not 3G, cell phone radiation affected resting EEG. Hung et al. (2007) showed that 2, 8, 217 Hz-modulated RFR differentially affected sleep. Lopez-Martin et al. (2009) reported that modulated and non-modulated RFR had different effects on gene expression in the brain. Nylund et al. (2010) found that different carrier-frequencies (900 MHz verses 1800 MHz) had different effects on protein expression. Schmid et al. (2012a) concluded that “modulation frequency components (of a RFR) within a physiological range may be sufficient to induce changes in sleep EEG”. Mohammed et al. (2013) reported that EEG power spectrum during REM sleep is more susceptible to modulated RFR than the slow-wave sleep (SWS). Schneider and Stangassinger (2014) reported different effects of 900-MHz and 1.966-GHz EMFs on social memory functions in the rat. Zhang et al. (2008) reported that an intermittent exposure to RFR had a more potent effect on gene expression in the brain than continuous exposure. Apparently, extremely-low frequency (ELF)-modulation plays a role on

determining the biological effects of RFR. One can find many studies showing the same neurological effects of RFR described above in animals exposed to extremely-low frequency electromagnetic field (ELF EMF) e.g., Carrubba et al., 2007, 2010; Cook et al., 2009; Cui et al., 2012; Perentos et al., 2008. This is of considerable importance, since all cell phone signals are modulated by low frequency components. Furthermore, effects can also depend on the modulation frequency. Bawin et al. (1975) reported an increase in efflux of calcium ions from chick brain tissue after 20 min of exposure to a 147-MHz RFR (1 to 2 mW/cm<sup>2</sup>). The effect occurred when the radiation was sinusoidally amplitude-modulated at 6, 9, 11, 16, or 20 Hz, but not at modulation frequencies of 0, 0.5, 3, 25, or 35 Hz. Blackman et al. (1979) also reported a “modulation-frequency window” in RFR-induced calcium ion efflux from brain tissue.

On the neurological effects of RFR, there are many papers published in the last decade indicating that oxidative stress played a role in the effects observed: Akbari et al., 2014; Bodera et al., 2015; Cetin et al., 2014; Dasdag et al., 2009, 2012; Del Vecchio et al., 2009a,b; Deshmukh et al., 2013a; Dragicevic et al., 2011; Eser et al., 2013; Gao et al., 2013; Ghazizadeh and Naziroglu, 2014; Hidisoglu et al., 2016; Hu S. et al., 2014; Hu et al., 2016; İkinici et al., 2016; Imge et al., 2010; Jing et al., 2012; Kerimoğlu et al., 2016a, b; Kesari et al., 2011; Kim JY et al., 2017; Liu et al., 2011; Maaroufi et al., 2014; Megha et al., 2012; Meral et al., 2007; Motawi et al., 2014; Narayanan et al., 2014; Nazıroğlu and Gümral, 2009; Nazıroğlu et al., 2012; Nirwane et al., 2016; Othman et al., 2017; Qin et al., 2014; Saikhedkar et al., 2014; Sharma et al., 2017; Shehu et al., 2016; Sokolovic et al., 2008; Varghese et al., 2017; Xu et al., 2010; Yang et al., 2010. (Dragicevic et al. (2011) reported a decrease in mitochondrial free radical production in the hippocampus and cerebral cortex of the mouse after RFR exposure.) There was one study (Poulletier de Gannes et al., 2011) that found no significant oxidative stress in brain cells after exposure to Enhanced Data rate for GSM Evolution (EDGE) signal. Kang et al (2014) reported that “neither combined RF radiation alone nor combined RF radiation with menadione or H<sub>2</sub>O<sub>2</sub> influences the intracellular reactive oxygen species (ROS) level in neuronal cells.” The mediating roles of cellular free radicals and oxidative status on the biological effects of EMF are worth looking into. Interestingly, there is a study (Cao et al., 2015) showing that RFR interacts with circadian rhythmicity on antioxidative processes in the rat.

An important issue that has been extensively debated in the media is whether children are more vulnerable to the effect of cell phone radiation than adults? The claim that children have thinner skulls and thus absorb more energy is not valid. And the claim that a child’s head absorbs more energy from a cell phone is also debatable. It is quite possible that the pattern of energy distribution of cell phone energy absorption in the head is significantly different between a child and an adult (cf. Christ and Kuster, 2005; Christ et al. 2010; Gandhi et al. 2012). Scientific data on whether a child is biologically more vulnerable to cell phone radiation is sparse. There are several studies that indicate that animals (including humans) of different ages respond differently to cell phone radiation. Bouji et al. (2012) reported differences in neuro-immunity, stress, and behavioral responses to GSM signals between ‘young adult’ (6 weeks-old) and ‘middle age’ (12-month old) rats. Croft et al. (2010) showed that GSM signals affected certain electrical activities of the brain in young human adults (19-40 years old) but not in adolescents (13-15 years old) or elderly (55-70 years old) subjects. Leung et al. (2011)

reported that performance in a cognitive test was affected by GSM signal in adolescents but not in young or old human subjects. Noor et al. (2011) reported differences in neurochemical responses to 900-MHz RFR between adult and young rats. And, Vecchio et al. (2010) found differences in brain electric activities between young and elderly human subjects responding to GSM signals. It must be pointed out that although these studies reported an age-dependent effect of cell phone radiation, they do not necessarily imply that children are more vulnerable to cell phone radiation than adults. There are several papers showing effects of exposure to RFR during perinatal periods on the development and functions of the nervous system (Aldad et al., 2012; Bas et al., 2013; Cetin et al., 2014; Daniels et al. 2009; Divan et al., 2008, 2011, 2012; Erdem Koç et al., 2016; Gao et al., 2013; Haghani et al., 2013; İkinici et al., 2013; Jing et al., 2012; Kokturk et al., 2013; Lee and Yang, 2014; Odaci et al., 2008, 2013, 2016; Othman et al., 2017; Ragbetli et al., 2010; Razavinasab et al., 2016; Zareen et al., 2009; Zhang et al., 2015). These studies point to the vulnerability of the development nervous system to RFR. The cerebellum seems to be a structure especially vulnerable to the exposure (Eser et al. 2013; Haghani et al., 2013; Kokturk et al., 2013; Odaci et al., 2016; Ragbetli et al., 2010). Chen et al. (2014) reported that exposure to an 1800-MHz RFR impaired neurite outgrowth of embryonic neural stem cells, which play a critical role in brain development. More recently, Xu et al. (2017) reported that effect of exposure to an 1800-MHz field on stem and progenitor cell proliferation in the hippocampus of mouse depended on the age of the animal. Stem cells play an important role in embryonic development. And, it turns out that they are very sensitive to electric current, particularly in their migration in the body during organogenesis. It has been suggested that electric current can be used as a guidance of migration of stem cells for the treatment of neurodegenerative diseases (Feng et al., 2017). On the other hand, disturbance of stem cells by induced electric currents of electromagnetic fields can cause defects in pre- and postnatal development. This can occur at low intensities of the field. Indeed, there are reports on effects of extremely-low frequency (ELF) magnetic and electric fields on stem cells (Bai et al., 2013; Choi et al., 2014; Cho et al., 2012; Kim et al., 2013; Takahashi et al., 2017). ELF EMF is more effective in generating induced electric currents.

With these physiological changes in the brain, what behavioral effects have been reported? Data are summarized in the tables below.

**Table 1. Behavioral Effects of Radiofrequency Radiation**

**Human studies that showed behavioral effects:**

	<b>Behavior studied/Results</b>	<b>Experimental conditions</b>
Danker-Hopfe et al. (2015)	Sleep of individuals affected differently- showing both improvements and deteriorations.	GSM 900 MHz and Wideband Code Division Multiple Access (WCDMA)/UMTS, during sleep
de Tommaso et al. (2009)	Reduction in behavioral	GSM 900 MHz, 10 min

	arousal	
Deniz et al. (2017)	Poorer attention in high exposure group	Low (<30 min/day) vs high (>90 min/day) cell phone radiation exposure
Hung et al. (2007)	Sleep latency	GSM 900 MHz with 2, 8, or 217-Hz modulations, 30 min
Leung et al. (2011)	Cognitive functions	2G and 3G cell phone radiation, 10 min
Luria et al. (2009)	Spatial working memory (In a subsequent study (Hareuveny et al., 2011), the authors indicated that some of the effects observed may not be related to RFR exposure.)	GSM phone, 60 min
Lustenberger et al. (2013)	Sleep-dependent motor-task performance improvement	0.25-0.8 Hz pulsed 900 MHz RFR, all-night
Mortazavi et al. (2012)	Decreased reaction time	Cell phone radiation, 10 min
Mortazavi et al. (2013)	Decreased reaction time; poorer short-term memory performance	Occupational exposure to military radar radiation
Movvahedi et al. (2014)	Better short-term memory in elementary school students	Cell phone radiation, 10 min
Redmayne et al. (2013)	Well-being	Use of cellphone and cordless phone
Regel et al. (2007)	Cognitive functions	pulse-modulated GSM 900 MHz signal, 0.2 or 5 W/kg, 30 min
Schoeni et al. (2015)	A change in memory performance	Based on cumulative duration of wireless phone use and RF-EMF dose over one year (GSM and UMTS)
Thomas et al. (2010)	Overall behavioral problems in adolescents	RFR measured by a personal dosimeter over 24 hr
Vecchio et al. (2012a)	Better performance in a	GSM signal at 902.4 MHz, 8.33

	cognitive- motor test	and 217 Hz modulations, peak SAR 0.5 W/kg, 45 min
Vecchio et al. (2012b)	Enhanced cognitive-motor processes in epileptic patients	GSM phone radiation, 45 min
Vecsei et al. (2013)	Decreased thermal pain perception	UMTS phone-like radiation, 1.75 W/kg, 30 min
Wiholm et al. (2009)	‘Virtual’ spatial navigation task	884 MHz, peak head SAR 1.4 W/kg, 150 min
Yogesh et al. (2014)	Sleep disturbance, latency and day dysfunction especially in females	> 2 hr/day of mobile phone use
Zheng et al. (2014)	Inattention in adolescents	Use of cell phone >60 min per day

**Human studies that showed no significant behavioral effects:**

	<b>Behavior studied</b>	<b>Experimental conditions</b>
Calvente et al. (2016)	No definite conclusion can be drawn on cognitive and behavioral functions of 10-year old boys	Environmental RFR 100 kHz to 6 GHz; root mean square 0.286 mW/cm <sup>2</sup> ; maximum power density 2.76 mW/cm <sup>2</sup>
Cinel et al. (2007)	Order threshold task	GSM or unmodulated carrier frequency wave to head, 40 min
Cinel et al. (2008)	Subjective symptoms	GSM or unmodulated carrier frequency wave to head, 40 min
Curcio et al. (2008)	Reaction time task, sequential figure tapping task	GSM (902.4 MHz, 217 Hz modulation, 0.5 W/kg), 3 x 15 min
Curcio et al. (2009)	objective and subjective vigilance	GSM (902.4 MHz, 8.33 Hz and 217-Hz modulation, 0.5 W/kg), 40 min
Curcio et al. (2012)	Somatosensory task	GSM (902.4 MHz, 8.33 Hz and 217-Hz modulation, 0.5

		W/kg), 40 min
Danker-Hopfe et al. (2011)	Effect on sleep	GSM 900 or WCDMA/UMTS, during sleep
Eltiti et al. (2009)	Cognitive functions	GSM 900 or UMTS, 0.001 mW/cm <sup>2</sup> , 50 min
Fritzer et al. (2007)	Sleep and cognitive functions	GSM900 with 2, 8, 217, 1733 Hz modulations, peak SAR within head 1 W/kg, during sleep
Haarala et al. (2007)	Cognitive functions	902 MHz, continuous-wave or pulsed (27 Hz, 0.577 ms), head peak SAR 1.18 W/kg, 90 min
Irlenbusch et al. (2007)	Visual discrimination threshold	GSM 902.4 MHz 217 Hz pulses, 0.1 mW/cm <sup>2</sup> , 30 min
Kleinlogel et al. (2008a)	Well being	1950 MHz UMTS (0.1 and 1 W/kg) or 900 MHz GSM (1 W/kg), 30 min
Kleinlogel et al. (2008b)	Continuous performance test measuring reaction time and false reaction	1950 MHz UMTS (0.1 and 1 W/kg) or 900 MHz GSM (1 W/kg), exposed during measurements
Krause et al. (2007)	Auditory memory task	902 MHz CW or pulsed at 217 Hz, pulse width 0.577 msec, averaged SAR 0.738 W/kg over 10 gm tissue, peak 1.18 W/kg
Kwon et al. (2010b)	Auditory sensory memory in children	GSM 902 MHz pulsed at 217 Hz, temporal lobe peak SAR 1.21 W/kg, average 0.82 W/kg over 10 gm tissue
Loughran et al. (2013)	Cognitive effects and EEG in 11-13 years old adolescences	Modulated GSM900 (peak SAR 1.4 W/kg or 0.35 W/kg), 30-60 min
Malek et al. (2015)	Cognitive functions in	Pulse-modulated GSM (945 MHz and 1840 MHz, 28

	sensitive humans	mW/cm <sup>2</sup> ) and UMTS (2140 MHz, 38 mW/cm <sup>2</sup> ), 1 V/m, whole body exposure, Short-term
Mohler et al. (2010, 2012)	Effect on sleep	Environmental far-field RFR and cell and cordless phone radiation
Nakatani-Enomoto et al. (2013)	Effect on sleep	W-CDMA, 3 hr
Redmayne et al. (2016)	Cognitive functions in 8-11 years old children	Use of cellular and cordless phone
Riddervold et al. (2008)	Trail making B test	2140 MHz continuous-wave and 2140 MHz modulated as UMTS, 45 min
Roser et al. (2016)	No change behavioral problem and concentration capacity	Self-reported and operator-recorded wireless communication device use
Sauter et al. (2011)	Cognitive functions	GSM900 and WCDMA, 7 hr 15 min in two episodes
Sauter et al. (2015)	Cognitive functions and well-being	Terrestrial Trunked Radio (TETRA) (385 MHz) signals, 2.5 hr
Schmid et al. (2012a)	Cognitive functions	900 MHz pulse modulated at 14 and 217 Hz, peak spatial SAR 2 W/kg, 30 min
Schmid et al. (2012b)	Cognitive functions	900 MHz pulse modulated at 2 Hz, 2 W/kg, 30 min
Trunk et al. (2013)	Automatic deviance detection processes	1947-MHz 3G UMTS, 1.75 W/kg 2 cm from surface of head model, 30 min
Trunk et al. (2014)	Reaction time to a stimulus	1947-MHz 3G UMTS signals, peak SAR 1.75 W/kg, 15 min
Trunk et al. (2015)	Reaction time to a visual target detection task	1947-MHz UMTS signals, peak SAR 1.75 W/kg, 15 min



Unterlechner et al. (2008)	attention	UMTS signals, peak SAR 0.63 W/kg at cortex of temporal lobe, 90 min
Wallace et al. (2012)	Cognitive functions	420 MHz TETRA, 0.001 mW/cm <sup>2</sup> , 10- 50 min, whole body exposure

#### Animal studies that showed behavioral effects:

	Behavior studied/results	Experimental conditions
Aldad et al. (2012)	Hyperactive, impaired memory (mouse)	800 and 1900 MHz cell phone radiation, gestation days 1-17 (24 hr/day), tested at 8, 12, and 16 weeks old
Arendash et al. (2010, 2012)	Improved cognitive behavior in mouse model of Alzheimer's disease	918 MHz pulse modulated at 217 Hz, 0.25-1.05 W/kg, 2-6 months or 12 days, 2 hr/day
Banaceur et al. (2013)	Improved cognitive functions in mouse model of Alzheimer's disease	2409 MHz, 1.6 W/kg, 2 hr/day for a month
Barthélémy et al. (2016)	Memory, emotionality, and locomotion in plus maze and open field (rat)	900 MHz modulated at 217 MHz, 15 min (1.5 or 6 W/kg) or 45 min (6 W/kg)
Bouji et al. (2012)	Contextual emotional behavior deficit (rat) (age-dependent effect observed)	900 MHz, 6 W/kg, 15 min
Cammaerts et al. (2012)	Olfactory and/or visual memory deficit in ants	GSM900 MHz (GSMK modulated), 0.77 V/m, in several periods 1.5-6 days
Cammaerts et al. (2013)	Deterioration of food collection behavior in ants	GSM900 MHz (GSMK modulated), 0.77 V/m, 180 hr
Cammaerts et al. (2014)	Changes in locomotor and general behaviors in ants	940 MHz pulse-modulated 577 $\mu$ s width, 0.5-1.5 V/m, 10 min exposure before

		behavioral observation
Choi and Choi (2016)	Delayed hyperactivity-like behavior (mouse)	Smart phone, 10 min/day, 9-11 weeks
Daniels et al. (2009)	Decreased motor activity and increased grooming (rat)	840 MHz, $6 \times 10^{-6}$ mW/cm <sup>2</sup> , pups exposed 3hr/day from postnatal day 2 to day14, tested at postnatal day 58
Deshmukh et al. (2013a)	Impaired cognitive functions (plus maze and water maze) (rat)	900 MHz, $8.47 \times 10^{-5}$ W/kg, 2 hr/day, 30 days
Deshmukh et al. (2015)	Impaired cognitive functions (plus maze and water maze) (rat)	900 MHz ( $5.953 \times 10^{-4}$ W/kg), 1800 MHz ( $5.835 \times 10^{-4}$ W/kg), 2450 MHz ( $6.672 \times 10^{-4}$ W/kg), 2 hr/day, 180 days
Deshmukh et al. (2016)	Impaired cognitive functions (plus maze and water maze) (rat)	900 MHz ( $5.953 \times 10^{-4}$ W/kg), 1800 MHz ( $5.835 \times 10^{-4}$ W/kg), 2450 MHz ( $6.672 \times 10^{-4}$ W/kg), 2 hr/day, 90 days
Favre (2011)	Induced piping behavior in honeybee workers	Cell phone put close to bee hive
Fragopoulou et al. (2010)	Spatial memory deficit (mouse)	GSM 900 MHz, 0.41-0.98 W/kg, 2 hr/day, 4 days
Hao et al. (2013)	Learning and memory deficit (rat)	916 MHz, 1 mW/cm <sup>2</sup> , 6 hr/day, 5 days/week, 10 weeks
Hassanshahi et al. (2017)	Impaired object recognition (rat)	2400 MHz, 12 hr/day, 30 days
Hu et al. (2014)	Spatial memory deficit (rat)	High power microwave, 30 mW/cm <sup>2</sup> , average brain SAR 21 W/kg, 15 min/day, 14 days
İkinci et al. (2013)	Learning and memory deficit (rat)	900 MHz, 13 <sup>th</sup> to 21 <sup>st</sup> day of pregnancy, 1 hr/day, offspring tested at 26 days old

Júnior et al. (2014)	Observed stress behavioral patterns (rat)	GSM 180 MHz, 2 V/m, 25 sec every 2 min for 3 days
Kim JH et al. (2017a)	Hyperactivity-like behavior (mouse)	835 MHz, 4 W/kg, 5 hr/day for 12 weeks
Kumar et al. (2009)	Hypoactivity, anxiety behavior (rat)	GSM 900 MHz and 1800 MHz, 50 missed call/day, 4 weeks
Kumari et al. (2017)	Spatial learning deficit and impairment of memory measured by passive avoidance test (mouse)	7.5 KHz magnetic field, 12 or 120 $\mu$ T, 5 weeks
Kumlin et al. (2007)	Improved spatial learning and memory (rat)	90 MHz, 0.3 or 3 W/kg, 2 hr/day, 5 days/week, 5 weeks
Lee et al. (2015)	Locomotor activity after feeding (fish <i>Poecilia reticulata</i> and <i>Danio rerio</i> )	RFR from an 1800 MHz cell phone
Li et al. (2015)	Spatial learning and memory deficits (rat)	2.856 MHz 5, 10, 20, or 30 mW/cm <sup>2</sup> , 6 min 3 times a week up to 6 weeks
Li et al. (2012)	Spatial learning and memory deficits (rat)	GSM 900 phone, 2 hr/day for 1 month, 0.52-1.08 W/kg
Lu et al. (2012)	Spatial memory deficit (rat)	2450 MHz pulsed, 1 mW/cm <sup>2</sup> , 3 hr/day, 30 days
Maaroufi et al. (2014)	Spatial learning and memory deficit (rat)	900 MHz, 0.05-0.18 W/cm <sup>2</sup> , 1 hr/day, 21 days
Mathur (2008)	Analgesic effect (rat)	73.5 MHz, amplitude-modulated at 16 Hz, 0.4 W/kg, 2 hr/day, 45 days
Megha et al. (2012)	Cognitive functions (plus maze and water maze) (rat)	900 MHz ( $5.953 \times 10^{-4}$ W/kg) or 1800 MHz ( $5.845 \times 10^{-4}$ W/kg), 2 hr/day, 30 days
Mohammed et al. (2013)	Increased latency of REM sleep (rat)	900 MHz continuous-wave, 900 MHz modulated at 8 and 16 Hz, spatial peak SAR 0.245

		W/kg, 1 hr/day for 1 month
Narayanan et al. (2009)	Spatial learning and memory deficit (rat)	GSM 900/1800 MHz, 50 missed call/day, 4 weeks
Narayanan et al. (2010)	Passive avoidance deficit (rat)	GSM 900/1800 MHz, 50 missed call/day, 4 weeks
Narayanan et al. (2013)	Elevated plus maze-emotionality test deficit (rat)	GSM 900 MHz phone, peak power density 0.1466 mW/cm <sup>2</sup> , 1 hr/day for 28 days
Narayanan et al. (2015)	Spatial memory deficit (rat)	GSM 900 MHz phone, peak power density 0.1466 mW/cm <sup>2</sup> , 1.15 W/kg, 1 hr/day for 28 days
Nirwane et al. (2016)	Change in social behavior, anxiety behavior, learning impairment (zebrafish)	GSM 900 MHz phone, 1.34 W/kg, 1 hr/day for 14 days
Nittby et al. (2008b)	Reduced memory functions (rat)	GSM 900 MHz, 0.0006 and 0.06 W/kg, 2 hr/week, 55 weeks
Ntzouni et al. (2011)	Non-spatial memory deficit (mouse)	GSM 1800-MHz phone, 0.22 W/kg, 90 min/day, 17 days
Ntzouni et al. (2013)	Spatial and non-spatial memory deficit (mouse)	GSM 1800-MHz phone, 0.11 W/kg, 90 min/day, 66-148 days
Odaci et al. (2013)	Motor function (rat)	900 MHz, 10 V/m, exposed 1 hr/day from day 13 to day 21 of pregnancy, offspring tested at 21 days of age
Othman et al. (2017)	Anxiety and deficits in neuromotor maturation mainly in male offspring (rat)	2450 MHz, 2 hr/day from conception to parturition, offspring tested at 28, 30 and 31 days of age
Pelletier et al. (2013)	Food intake increase; changes in sleep parameters; increased food intake (rat)	900 MHz, 1 V/m, 0.3-0.1 W/kg depending on age, 23.5 hr/day, 5 weeks

Pelletier et al. (2014)	Preferred to sleep in a different temperature environment than controls; sleep parameters (rat)	900 MHz, 1 V/m, 0.3-0.1 W/kg depending on age, 23.5 hr/day, 5 weeks
Qiao et al. (2014)	Spatial memory deficit (rat)	2856 MHz, 30 mW/cm <sup>2</sup> , 14 W/kg, 5 min
Qin et al. (2014)	Learning and memory deficits (mouse)	1800 MHz, 0.208 mW/cm <sup>2</sup> , 2 hr/day, 30 days
Razavinasab et al. (2016)	Passive avoidance and spatial learning and memory deficits (rat)	900 MHz pulsed RFR, 0.3-0.9 W/kg, 6hr/day from conception to birth, tested at 30 days of age
Saikhedkar et al. (2014)	Learning and memory deficits (rat)	900 MHz phone, 0.9 W/kg, 4 hr/day, 15 days
Sarapultseva et al. (2014)	Motor activity (protozoa Spirostomum ambiguum)	1000 MHz Or 10,000 MHz, 0.005-0.05 mW/cm <sup>2</sup> , 0.05-10 hr
Schneider and Stangassinger (2014)	Social memory effect (rat)	GSM 900 MHz and UMTS 1966 MHz, 0.4 W/kg, up to 6 months
Sharma et al. (2014)	Spatial learning memory deficit (mouse)	10,000 MHz, 0.25 mW/cm <sup>2</sup> , 0.179 W/kg, 2 hr/day, 30 days
Sharma et al. (2017)	Spatial learning and memory deficit (mouse)	10,000 MHz, 0.25 mW/cm <sup>2</sup> , 0.179 W/kg, 2 hr/day, 15 days
Shehu et al. (2016)	Anxiety-like behavior (rat)	GSM 900/1800 phones, 10 min call per day for 4 weeks
Sokolovic et al. (2012)	Anxiety-related behavior (rat)	GSM900 phone, 9.88-13.356 V/m, 0.43-0.135 W/kg, 4 hr/day for 20, 40, 60 days
Tang et al. (2015)	Spatial long-term memory deficit (rat)	900 MHz, 1 mW/cm <sup>2</sup> , 0.016 W/kg, 3 hr/day for 14-28 days

Vácha et al. (2009)	Magnetoreception disruption (cockroach)	Onset of disruption: 1.2 MHz 12-18 nT; 2.4 MHz 18-44 nT
Varghese et al. (2017)	Learning and memory deficits and expression of anxiety behavior (rat)	2450 MHz, 4 hr/day for 45 days; at power density of 0.778 mW/cm <sup>2</sup> , calculated power absorption in the body = 0.04728 W
Wang H. et al. (2013)	Spatial memory deficit (rat)	Pulsed 2856 MHz RFR, 5, 10, and 50 mW/cm <sup>2</sup> , 6 min
Wang H. et al. (2015)	Spatial learning and memory deficits (rat)	Pulsed 2856 MHz RFR, 50 mW/cm <sup>2</sup> , 6 min
Wang H. et al. (2017)	Spatial learning and memory deficits (rat)	2856 MHz (1.75, 3.5, or 7 W/kg), 6 min/day, 5 days/week, 6 weeks
Wang K. et al. (2017)	Increased recognition memory (mouse)	1800 MHz, >2.2 W/kg, 30 min
Wang LF et al. (2016)	Spatial memory impairment (rat)	GSM 1800 MHz, 30 mW/cm <sup>2</sup> , 5 min/day, 5 days /week, 2 months
Zhang et al. (2015)	Increased anxiety-related behavior; spatial memory and learning deficits in male offspring (mouse)	9417 MHz, 200 V/m, 2 W/kg, 12 hr/day on gestation days 3.5-18, offspring tested at 5 weeks of age
Zhang et al. (2017)	Increased anxiety-related behavior (mouse)	1800 MHz, 6 hr/day for 28 days, whole body and brain SAR at 2.7 W/kg and 2.2 W/kg, respectively

**Animal studies that showed no significant behavioral effects:**

	<b>Behavior studied</b>	<b>Experimental conditions</b>
Ammari et al. (2008c)	spatial memory (rat)	GSM900, brain SRR 1.5 W/kg 45 min/day or 6 W/kg 15

		min/day, 8 or 24 weeks
Fasseas et al. (2015)	Chemotaxis, short-term memory ( <i>Caenorhabditis elegans</i> )	GSM 1800 MHz (15.4 V/m), WiFi router (9.7 V/m), Digital Enhanced Cordless Telecommunication (DECT) phone (11.3 V/m); various lengths of time (30 min to 24 hr)
Haghani et al. (2013)	Motor function (rat)	Pulsed 900MHz RFR, SAR 0.5-0.9 W/kg; 6 hr/day during gestation period
Klose et al. (2014)	Learning skills and motor behavior (rat)	GSM-modulated 900 MHz RFR, head only exposure 2 hr/day, 5 days/week from 14 days to 19 months old, 0.7, 2.5 or 10 W/kg
Shirai et al. (2014)	Spatial memory and motor function on F <sub>1</sub> , F <sub>2</sub> , and F <sub>3</sub> offspring (rat)	2140 MHz WCDMA 20 hr/day from gestation Day 7 to weaning with dam, and offspring alone to 6 weeks old, 3-generations; 0.067-0.14 for a fetus, 0.12-0.36 W/kg for offspring before weaning, 0.12-0.24 W/kg for offspring after weaning
Salunke et al. (2015)	Anxiety, obsessive compulsive disorder (OCD) and depression-like behavior (mouse)	Bluetooth device, 2450 MHz, 60 min/day for 7, 30, 60, 90, or 120 days
Son et al. (2016)	Spatial and non-spatial memory functions (mouse)	1950 MHz; 2 h/day, 5 days/week, 3 months; 5 W/kg

A majority of the animal studies reported effects, whereas more human studies reported no significant effects than effects. This may be caused by several possible factors: (a) Humans are less susceptible to RFR than are animals. (b) It may be more difficult to do human than animal experiments, since it is, in general, easier to control the variables and confounding factors in an animal experiment. (c) In the animal studies, the cumulative exposure duration was generally longer and studies were carried out after exposure, whereas in the human studies, the exposure was generally one time and testing was measurements were carried out



mostly during exposure. This raises the question of whether the effects of RFR are cumulative. This consideration could have very important implication on real life human exposure to EMF. However, it must be pointed out that neurophysiological and behavioral changes have been reported in both animals and humans after acute (one time) exposure to RFR, and most of the human EEG studies mentioned above are acute exposure experiments. (d) Most of the human studies are head exposure experiments whereas most of the animal studies involved whole body exposure. Could this have made a difference? Does it mean that effects of RFR on other parts of the body can also affect the nervous system? (e) The nervous system has the capability to adapt to perturbations. Physiological changes in the nervous system do not always manifest as behavioral effects, e.g., see Haghani et al. (2013) (changes in electrophysiology of cerebellar Purkinje cells after RFR exposure without behavioral effect in rats) and Schmid et al. (2012a) (RFR exposure induced EEG change but did not affect cognitive test performance in human subjects). May be the human brain has higher capability to tolerate and adapt to perturbations than other animals. (f) In the animal studies, the effects studies were mostly learning and memory functions. The hippocampus in the brain, particularly the cholinergic system, plays a major role in learning and memory functions. Various studies indicated that RFR affected electrical activities/morphology/chemistry of the hippocampus in animals (Aboul Ezz et al., 2013; Ammari et al., 2008 a, b; 2010; Barcal and Vozeh, 2007; Barthélémy et al., 2016; Baş et al., 2009, 2013; Carballo-Quintas et al., 2011; Choi and Choi, 2016; Erdem Koç et al., 2016; Fragopoulous et al., 2012; Gevrek, 2017; Gökçek-Saraç et al., 2017; Hao et al., 2013; Hassanshahi et al., 2017; Hu et al., 2014; İkinci et al., 2013; Kerimoğlu et al., 2016b; Kesari et al., 2011; Kim JH et al., 2017b; Kim JY et al., 2017; Kumari et al., 2017; Li et al., 2014; Lopez-Martin et al., 2009; Li et al., 2012; Lu et al., 2012; Maskey et al., 2010 a,b, 2012; Megha et al., 2015; Mugunthan et al., 2016; Narayanan et al., 2010, 2014, 2015; Ning et al., 2007; Nittby et al., 2008a; Odaci et al., 2008; Razavinasab et al., 2016; Şahin et al., 2015; Saikhedkar et al., 2014; Sharma et al., 2017; Tang et al., 2015; Tong et al., 2013; Wang H. et al., 2013, 2015, 2017; Wang K. et al., 2017; Wang LF et al., 2016; Xiong et al. 2015; Xu et al., 2017; Yang et al., 2012; Zhang et al., 2017). As early as 1987, we (Lai et al., 1987) have reported that RFR affected the cholinergic system in the hippocampus of the rat leading to spatial learning and memory deficits. Interestingly, the effect of RFR on the hippocampus apparently involves a sequence of neurological responses in the brain, including activation of endogenous opioids and release of the stress hormone corticotropin releasing factor (Lai, 1994). Thus, it is not surprising that 'learning and memory' functions are affected in the rodents by RFR since in most of the studies, the Morris water-maze was used to study learning and memory functions. The water-maze measures spatial memory, a function specifically involves the hippocampus. In the human studies listed above, the most common effect studied was cognitive functions. Since the exposure in most of these human studies was localized in the brain, particularly in the temporal cortical area, it is questionable whether the psychological tests used were appropriate.

## Discussion

1. A major concern is that in some of the studies details of the exposure setup and dosimetry are not provided. This is important, since details of the independent variables

are very important in interpreting the validity of the experimental results, i.e., dependent variables. In many of these studies, a cell phone was used in the exposure of animals and humans. But information on how the cell phone was activated, in many instances, was not provided. Thus, the amount of energy deposited in the body was not known. Some studies used the phone in 'stand-by' mode. Mild et al. (2012) reported that when a stationary cell phone is on 'stand-by' mode, it actually infrequently emits a very small amount of energy. It is very surprising that in all papers on the effects of RFR on EEG mentioned at the beginning of this paper, only two provided significant information on the exposure parameters. This is alarming. It may indicate that the researchers did not understand the properties of the entity that they were studying. It is good that competent researchers from other disciplines are contributing to the advancement of bioelectromagnetics. But, I sincerely think that EMF researchers should get themselves acquainted with the physics of nonionizing electromagnetic fields.

2. Most of the studies were carried out with relatively high levels of RFR compared to environmental level. However, if you look through the narrative about, there are studies that reported effects at very low level, e.g., Bak et al, 2010. Indeed, biological/health effects of RFR at levels much lower than most international RFR-exposure guidelines, e.g., the International Commission on Non-ionizing Radiation Protection (ICNIRP), have been reported (see Table 1 in Levitt and Lai, 2010). This raises the question on whether the guidelines used in most countries nowadays are actually obsolete and new exposure guidelines have to be set.
3. Thus, there is ample evidence that RFR exposure affects the nervous system from both acute and long-term exposure experiments. Brain electric activities, nerve cell functions and chemistry and behavior can be affected. Some explanatory mechanisms for these effects have emerged. One consistent finding is that animals exposed RFR suffered from memory and learning deficits. These effects can be explained by the results of numerous reports that showed RFR affected the hippocampus, a brain region involved in memory and learning. However, the location and configuration of the human hippocampus are quite different from those of a rodent. There has not been much studies on the effect of RFR on the human hippocampus. Several studies did reported deficit in memory in human subjects exposed to RFR, particularly on short-term memory, a function specifically related to the hippocampus. One recent study (Deniz et al., 2017) showed that chronic cell phone use did not significantly affect the volume of the hippocampus in human subjects. But, the subjects showed poorer attention which is probably not related to the hippocampus. An interesting fact is that learning and memory deficits have also been reported in insects that do not have a hippocampus. Another related aspect is that several papers (Adrendash et al., 2010, 2012; Banaceur et al., 2013; Dragicevic et al., 2011) have indicated that RFR exposure could reverse some of the

defects in an animal model of Alzheimer's disease, a neurological disorder involved degeneration of cholinergic innervations in the hippocampus. Interestingly, similar claim has been reported (Hu et al., 2016) with exposure to extremely-low frequency magnetic field.

4. Another very consistent finding is that RFR affects free radical metabolism in the brain. This may explain some of the cellular and physiological effects of RFR on the nervous system. As a matter of fact, oxidative changes in cells and tissues after exposure to RFR is a very common phenomenon (cf. Yakymenko et al., 2016). This happened in many organs of the body and can provide explanation on many reported biological effects of RFR.
5. Many of the effects of RFR on the nervous system, e.g., on the hippocampus, oxidative effect, and behavioral effects, are also observed with exposure to extremely-low frequency electromagnetic field (cf. my section on the neurological effects of ELF EMF in the Bioinitiative Report, [www.bioinitiative.info/bioInitiativeReport2012.pdf](http://www.bioinitiative.info/bioInitiativeReport2012.pdf)). There has been speculation whether biological effects observed with low-frequency modulated-RFR were actually caused by the modulation. There are two reports published in the last decade that seemed to refute this hypothesis. Perentos et al. (2013) reported in human EEG "...a suppression of the global alpha band activity was observed under the pulsed modulated RF exposure, and this did not differ from the continuous RF exposure. No effect was seen in the extremely low frequency condition." This means that pulsing is not essential for the effect observed. Schmid et al. (2012b) compared the effects of a 2-Hz modulated 900-MHz field with a 2-Hz magnetic field on human sleep EEG. Both fields affect sleep EEG but not identically. The authors concluded that "the study does not support the hypothesis that effects of radiofrequency exposure are based on demodulation of the signal only." However, in another study, Schmid et al (2012a) concluded in a study on sleep EEG that "...that modulation frequency components within a physiological range may be sufficient to induce these effects." In our earlier studies (e.g., Lai and Singh, 1995), we found that continuous-wave and pulsed RFR produced different effects. Indeed, different effects produced by continuous-wave and modulated RFR with the same frequency, exposure conditions, and SAR is a strong indication of the existence of "nonthermal" effects. Another question is whether one type of modulation is different from another in causing biological effects. Cell phone advances from one generation to another. Do the research data of 3G phone apply to 4G or 5G phone radiation? RFR is a complex entity. Its biological effects depend on many of its physical properties, e.g., frequency, direction of the incident waves relative to the object exposed, dielectric properties and size and shape of the exposed object, polarization of the waves, etc. Thus, it is unlikely that one can easily extrapolate the effects from one form of RFR to another. An assumption that 3G radiation is safe does

not necessary imply that 5G radiation is safe. Each one of them has to be investigated separately.

6. An important area of research is on how RFR in the environment affects humans and wildlife. Environmental RFR level has become higher and higher over the past decades due to the employment of RFR-wireless devices. Take the example of Bak et al. (2010) mentioned above, effect on human event-related brain potential was reported after 20 min of exposure to a GSM signal at a power density of  $0.0052 \text{ mW/cm}^2$ . This is very close to the levels found in some cities. The highest power density of ambient RFR measured near schools and Hospitals in Chandigarh, India was reported to be  $0.001148 \text{ mW/cm}^2$  in 2012 (Dhami, 2012). The maximum total RFR power density emitted by FM and TV broadcasting stations and mobile phone base stations in centers of the major cities in the West Bank-Palestine was  $0.00386 \text{ mW/cm}^2$  (Lahham and Hammash, 2012). One also has to take into consideration that exposure in the Bak et al. (2010) study was acute (20 min), whereas environmental exposure is chronic. Related to the neurological effect is the magnetic-sense possessed by many species of animals. It is essential for their survival. Interference by RFR of magnetic compass orientation in animals has been reported (e.g., Landler et al., 2015; Malkemper et al., 2015; Pakhomov et al., 2017; Schwarze et al., 2016; Vácha et al., 2009). Understanding the effects could help in preserving the ecosystem and ensure survival of the species on this earth.

## References

Aboul Ezz HS, Khadrawy YA, Ahmed NA, Radwan NM, El Bakry MM. The effect of pulsed electromagnetic radiation from mobile phone on the levels of monoamine neurotransmitters in four different areas of rat brain. *Eur Rev Med Pharmacol Sci*. 17:1782-1788, 2013.

Abramson MJ, Benke GP, Dimitriadis C, Inyang IO, Sim MR, Wolfe RS, Croft RJ. Mobile telephone use is associated with changes in cognitive function in young adolescents. *Bioelectromagnetics*. 30:678-686, 2009.

Akbari A, Jelodar G, Nazifi S. Vitamin C protects rat cerebellum and encephalon from oxidative stress following exposure to radiofrequency wave generated by a BTS antenna model. *Toxicol Mech Methods*. 24:347-352, 2014.

Aldad TS, Gan G, Gao XB, Taylor HS. Fetal radiofrequency radiation exposure from 800-1900 MHz-rated cellular telephones affects neurodevelopment and behavior in mice. *Sci Rep*. 2:312, 2012.

- Ammari M, Brillaud E, Gamez C, Lecomte A, Sakly M, Abdelmelek H, de Seze R. Effect of a chronic GSM 900 MHz exposure on glia in the rat brain. *Biomed Pharmacother.* 62:273-281, 2008a.
- Ammari M, Lecomte A, Sakly M, Abdelmelek H, de-Seze R. Exposure to GSM 900 MHz electromagnetic fields affects cerebral cytochrome c oxidase activity. *Toxicol.* 250:70-74, 2008b.
- Ammari M, Jacquet A, Lecomte A, Sakly M, Abdelmelek H, de Seze R. Effect of head-only sub-chronic and chronic exposure to 900-MHz GSM electromagnetic fields on spatial memory in rats. *Brain Inj.* 22:1021-1029, 2008c.
- Ammari M, Gamez C, Lecomte A, Sakly M, Abdelmelek H, De Seze R. GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field signal. *Int J Radiat Biol.* 86:367-375, 2010.
- Arendash GW, Sanchez-Ramos J, Mori T, Mamcarz M, Lin X, Runfeldt M, Wang L, Zhang G, Sava V, Tan J, Cao C. Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. *J Alzheimers Dis.* 19:191-210, 2010.
- Arendash GW, Mori T, Dorsey M, Gonzalez R, Tajiri N, Borlongan C. Electromagnetic treatment to old Alzheimer's mice reverses  $\beta$ -amyloid deposition, modifies cerebral blood flow, and provides selected cognitive benefit. *PLoS One.* 7:e35751, 2012.
- Arns M, Van Luitelaar G, Sumich A, Hamilton R, Gordon E. Electroencephalographic, personality, and executive function measures associated with frequent mobile phone use. *Int J Neurosci.* 117:1341-1360, 2007.
- Bai WF, Xu WC, Feng Y, Huang H, Li XP, Deng CY, Zhang MS. Fifty-Hertz electromagnetic fields facilitate the induction of rat bone mesenchymal stromal cells to differentiate into functional neurons. *Cytotherapy.* 15:961-970, 2013.
- Bak M, Dudarewicz A, Zmyślony M, Sliwinska-Kowalska M. Effects of GSM signals during exposure to event related potentials (ERPs). *Int J Occup Med Environ Health.* 23:191-199, 2010.
- Banaceur S, Banasr S, Sakly M, Abdelmelek H. Whole body exposure to 2.4 GHz WIFI signals: effects on cognitive impairment in adult triple transgenic mouse models of Alzheimer's disease (3xTg-AD). *Behav Brain Res.* 240:197-201, 2013.
- Barcal J, Vozeh F. Effect of whole-body exposure to high-frequency electromagnetic field on the brain cortical and hippocampal activity in mouse experimental model. *NeuroQuantology* 5:292-302, 2007.

Barthélémy A, Mouchard A, Bouji M, Blazy K, Puigsegur R, Villégier AS. Glial markers and emotional memory in rats following acute cerebral radiofrequency exposures. *Environ Sci Pollut Res Int*. 23:25342-25355, 2016.

Bas O, Odaci E, Kaplan S, Acer N, Uçok K, Colakoglu S. 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat. *Brain Res*. 1265:178-185, 2009.

Baş O, Sönmez OF, Aslan A, İkinci A, Hancı H, Yıldırım M, Kaya H, Akça M, Odacı E. Pyramidal cell loss in the cornu ammonis of 32-day-old female rats following exposure to a 900 megahertz electromagnetic field during prenatal days 13–21. *NeuroQuantology* 11:591-599, 2013.

Bawin SM, Kaczmarek LK, Adey WR. Effects of modulated VHF fields on the central nervous system. *Annals NY Acad Sci*. 247:74-81, 1975.

Blackman CF, Elder JA, Weil CM, Benane SG, Eichinger DC, House DE. Induction of calcium-ion efflux from brain tissue by radio-frequency radiation: effects of modulation frequency and field strength. *Radio Sci*. 14(6S):93-98, 1979.

Bodera P, Stankiewicz W, Antkowiak B, Paluch M, Kieliszek J, Sobiech J, Niemcewicz M. Influence of electromagnetic field (1800 MHz) on lipid peroxidation in brain, blood, liver and kidney in rats. *Int J Occup Med Environ Health*. 28:751-759, 2015.

Bouji M, Lecomte A, Hode Y, de Seze R, Villégier AS. Effects of 900 MHz radiofrequency on corticosterone, emotional memory and neuroinflammation in middle-aged rats. *Exp Gerontol*. 47:444-451, 2012.

Bhagat S, Varshney S, Bist SS, Goel D, Mishra S, Jha VK. Effects on auditory function of chronic exposure to electromagnetic fields from mobile phones. *Ear Nose Throat J*. 95:E18-22, 2016.

Brillaud E, Piotrowski A, de Seze R. Effect of an acute 900 MHz GSM exposure on glia in the rat brain: a time-dependent study. *Toxicology*. 238:23-33, 2007.

Calvente I, Pérez-Lobato R, Núñez MI, Ramos R, Guxens M, Villalba J, Olea N, Fernández MF. Does exposure to environmental radiofrequency electromagnetic fields cause cognitive and behavioral effects in 10-year-old boys? *Bioelectromagnetics*. 37:25-36, 2016.

Cammaerts MC, De Doncker P, Patris X, Bellens F, Rachidi Z, Cammaerts D. GSM 900 MHz radiation inhibits ants' association between food sites and encountered cues. *Electromagn Biol Med*. 31:151-165, 2012.

Cammaerts MC, Rachidi Z, Bellens F, De Doncker P. Food collection and response to pheromones in an ant species exposed to electromagnetic radiation. *Electromagn Biol Med*. 32:315-332, 2013.

Cammaerts M-C, Vandenbosch GAE, Volski V. Effect of short-term GSM radiation at representative levels in society on a biological model: the ant *Myrmica sabuleti*. *J Insect Beh.* 27:514-526. 2014.

Cao H, Qin F, Liu X, Wang J, Cao Y, Tong J, Zhao H. Circadian rhythmicity of antioxidant markers in rats exposed to 1.8 GHz radiofrequency fields. *Int J Environ Res Public Health.* 12:2071-2087, 2015.

Carballo-Quintás M, Martínez-Silva I, Cadarso-Suárez C, Alvarez-Figueiras M, Ares-Pena FJ, López-Martín E. A study of neurotoxic biomarkers, c-fos and GFAP after acute exposure to GSM radiation at 900 MHz in the picrotoxin model of rat brains. *Neurotoxicology.* 32:478-494, 2011.

Carrubba S, Frilot C, Chesson AL, Marino AA. Nonlinear EEG activation evoked by low-strength low-frequency magnetic fields. *Neurosci Lett.* 417:212-216, 2007.

Carrubba S, Frilot C 2nd, Chesson AL Jr, Marino AA. Mobile-phone pulse triggers evoked potentials. *Neurosci Lett.* 469:164-168, 2010.

Çeliker M, Özgür A, Tümkaya L, Terzi S, Yılmaz M, Kalkan Y, Erdoğan E. Effects of exposure to 2100 MHz GSM-like radiofrequency electromagnetic field on auditory system of rats. *Braz J Otorhinolaryngol.* 83:691-696, 2017.

Cetin H, Nazıroğlu M, Celik O, Yüksel M, Pastacı N, Ozkaya MO. Liver antioxidant stores protect the brain from electromagnetic radiation (900 and 1800 MHz)-induced oxidative stress in rats during pregnancy and the development of offspring. *J Matern Fetal Neonatal Med.* 27:1915-1921, 2014.

Chen C, Ma Q, Liu C, Deng P, Zhu G, Zhang L, He M, Lu Y, Duan W, Pei L, Li M, Yu Z, Zhou Z. Exposure to 1800 MHz radiofrequency radiation impairs neurite outgrowth of embryonic neural stem cells. *Sci Rep.* 4:5103, 2014.

Cho H, Seo YK, Yoon HH, Kim SC, Kim SM, Song KY, Park JK. Neural stimulation on human bone marrow-derived mesenchymal stem cells by extremely low frequency electromagnetic fields (ELF-EMFs). *Biotechnol Prog.* 28:1329-1335, 2012.

Choi Y-J, Choi Y-S. Effects of electromagnetic radiation from smartphones on learning ability and hippocampal progenitor cell proliferation in mice. *Osong Pub Health Res Persp.* 7:12-17, 2016.

Choi YK, Lee DH, Seo YK, Jung H, Park JK, Cho H. Stimulation of neural differentiation in human bone marrow mesenchymal stem cells by extremely low-frequency electromagnetic fields incorporated with MNPs. *Appl Biochem Biotechnol.* 174:1233-1245, 2014.



- Christ A, Kuster N. Differences in RF energy absorption in the heads of adults and children. *Bioelectromagnetics*. Suppl 7:S31-44, 2005.
- Christ A, Gosselin MC, Christopoulou M, Kühn S, Kuster N. Age-dependent tissue-specific exposure of cell phone users. *Phys. Med. Biol.* 55:1767-1783, 2010.
- Cinel C, Boldini A, Russo R, Fox E. Effects of mobile phone electromagnetic fields on an auditory order threshold task. *Bioelectromagnetics*. 28:493-496, 2007.
- Cinel C, Russo R, Boldini A, Fox E. Exposure to mobile phone electromagnetic fields and subjective symptoms: a double-blind study. *Psychosom Med.* 70:345-348, 2008.
- Cook CM, Saucier DM, Thomas AW, Prato FS. Changes in human EEG alpha activity following exposure to two different pulsed magnetic field sequences. *Bioelectromagnetics*. 30:9-20, 2009.
- Croft RJ, Hamblin DL, Spong J, Wood AW, McKenzie RJ, Stough C. The effect of mobile phone electromagnetic fields on the alpha rhythm of human electroencephalogram. *Bioelectromagnetics*. 29:1-10, 2008.
- Croft RJ, Leung S, McKenzie RJ, Loughran SP, Iskra S, Hamblin DL, Cooper NR. Effects of 2G and 3G mobile phones on human alpha rhythms: Resting EEG in adolescents, young adults, and the elderly. *Bioelectromagnetics*. 31:434-444, 2010.
- Cui Y, Ge Z, Rizak JD, Zhai C, Zhou Z, Gong S, Che Y. Deficits in water maze performance and oxidative stress in the hippocampus and striatum induced by extremely low frequency magnetic field exposure. *PLoS One*. 7:e32196, 2012.
- Curcio G, Valentini E, Moroni F, Ferrara M, De Gennaro L, Bertini M. Psychomotor performance is not influenced by brief repeated exposures to mobile phones. *Bioelectromagnetics*. 29:237-241, 2008.
- Curcio G, Ferrara M, Limongi T, Tempesta D, Di Sante G, De Gennaro L, Quaresima V, Ferrari M. Acute mobile phones exposure affects frontal cortex hemodynamics as evidenced by functional near-infrared spectroscopy. *J Cereb Blood Flow Metab.* 29:903-910, 2009.
- Curcio G, Nardo D, Perrucci MG, Pasqualetti P, Chen TL, Del Gratta C, Romani GL, Rossini PM. Effects of mobile phone signals over BOLD response while performing a cognitive task. *Clin Neurophysiol.* 123:129-136, 2012.
- Daniels WM, Pitout IL, Afullo TJ, Mabandla MV. The effect of electromagnetic radiation in the mobile phone range on the behaviour of the rat. *Metab Brain Dis.* 24:629-641, 2009.
- Danker-Hopfe H, Dorn H, Bahr A, Anderer P, Sauter C. Effects of electromagnetic fields emitted by mobile phones (GSM 900 and WCDMA/UMTS) on the macrostructure of sleep. *J Sleep Res.* 20(1 Pt 1):73-81, 2011.

Danker-Hopfe H, Dorn H, Bolz T, Peter A, Hansen ML, Eggert T, Sauter C. Effects of mobile phone exposure (GSM 900 and WCDMA/UMTS) on polysomnography based sleep quality: An intra- and inter-individual perspective. *Environ Res.* 145:50-60, 2015.

Dasdag S, Akdag MZ, Ulukaya E, Uzunlar AK, Ocak AR. Effect of mobile phone exposure on apoptotic glial cells and status of oxidative stress in rat brain. *Electromagn Biol Med.* 28:342-354, 2009.

Dasdag S, Akdag MZ, Kizil G, Kizil M, Cakir DU, Yokus B. Effect of 900 MHz radio frequency radiation on beta amyloid protein, protein carbonyl, and malondialdehyde in the brain. *Electromagn Biol Med.* 31:67-74, 2012.

de Gannes FP, Billaudel B, Taxile M, Haro E, Ruffié G, Lévêque P, Veyret B, Lagroye I. Effects of head-only exposure of rats to GSM-900 on blood-brain barrier permeability and neuronal degeneration. *Radiat Res.* 172:359-367, 2009.

de Tommaso M, Rossi P, Falsaperla R, Francesco Vde V, Santoro R, Federici A. Mobile phones exposure induces changes of contingent negative variation in humans. *Neurosci Lett.* 464:79-83, 2009.

Del Vecchio G, Giuliani A, Fernandez M, Mesirca P, Bersani F, Pinto R, Ardoino L, Lovisolo GA, Giardino L, Calzà L. Effect of radiofrequency electromagnetic field exposure on in vitro models of neurodegenerative disease. *Bioelectromagnetics.* 30:564-572, 2009.

Del Vecchio G, Giuliani A, Fernandez M, Mesirca P, Bersani F, Pinto R, Ardoino L, Lovisolo GA, Giardino L, Calzà L. Continuous exposure to 900MHz GSM-modulated EMF alters morphological maturation of neural cells. *Neurosci Lett.* 455:173-177, 2009.

Deniz OG, Kaplan S, Selcuk MB, Terzi M, Altun, Yurt KK, Aslan K, Davis D. Effects of short and long term electromagnetic fields exposure on the human hippocampus. *J Micros Ultrastru.* 5:191-197, 2017.

Deshmukh PS, Banerjee BD, Abegaonkar MP, Megha K, Ahmed RS, Tripathi AK, Mediratta PK. Effect of low level microwave radiation exposure on cognitive function and oxidative stress in rats. *Indian J Biochem Biophys.* 50:114-119, 2013.

Deshmukh PS, Nasare N, Megha K, Banerjee BD, Ahmed RS, Singh D, Abegaonkar MP, Tripathi AK, Mediratta PK. Cognitive impairment and neurogenotoxic effects in rats exposed to low-intensity microwave radiation. *Int J Toxicol.* 34:284-290, 2015.

Deshmukh PS, Megha K, Nasare N, Banerjee BD, Ahmed RS, Abegaonkar MP, Tripathi AK, Mediratta PK. Effect of low level subchronic microwave radiation on rat brain. *Biomed Environ Sci.* 29:858-867, 2016.

Dhami AK. Study of electromagnetic radiation pollution in an Indian city. *Environ Monit Assess.* 184:6507-6512, 2012.

Divan HA, Kheifets L, Obel C, Olsen J. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. *Epidemiology.* 19:523-529, 2008.

Divan HA, Kheifets L, Olsen J. Prenatal cell phone use and developmental milestone delays among infants. *Scand J Work Environ Health.* 37:341-348, 2011.

Divan HA, Kheifets L, Obel C, Olsen J. Cell phone use and behavioural problems in young children. *J Epidemiol Community Health.* 66:524-529, 2012.

Dragicevic N, Bradshaw PC, Mamcarz M, Lin X, Wang L, Cao C, Arendash GW. Long-term electromagnetic field treatment enhances brain mitochondrial function of both Alzheimer's transgenic mice and normal mice: a mechanism for electromagnetic field-induced cognitive benefit? *Neuroscience* 185:135-149, 2011.

Eberhardt JL, Persson BR, Brun AE, Salford LG, Malmgren LO. Blood-brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones. *Electromagn Biol Med.* 27:215-229, 2008.

Eltiti S, Wallace D, Ridgewell A, Zougkou K, Russo R, Sepulveda F, Fox E. Short-term exposure to mobile phone base station signals does not affect cognitive functioning or physiological measures in individuals who report sensitivity to electromagnetic fields and controls. *Bioelectromagnetics.* 30:556-563, 2009.

Erdem Koç G, Kaplan S, Altun G, Gümüş H, Gülsüm Deniz Ö, Aydın I, Emin Onger M, Altunkaynak Z. Neuroprotective effects of melatonin and omega-3 on hippocampal cells prenatally exposed to 900 MHz electromagnetic fields. *Int J Radiat Biol.* 92:590-595, 2016.

Eser O, Songur A, Aktas C, Karavelioglu E, Caglar V, Aylak F, Ozguner F, Kanter M. The effect of electromagnetic radiation on the rat brain: an experimental study. *Turk Neurosurg.* 23:707-715, 2013.

Fasseas MK, Fragopoulou AF, Manta AK, Skouroliahou A, Vekrellis K, Margaritis LH, Syntichaki P. Response of *Caenorhabditis elegans* to wireless devices radiation exposure. *Int J Radiat Biol.* 91:286-293, 2015.

Favre D. Mobile phone-induced honeybee worker piping. *Apidologie* 42:270–279, 2011.

Feng JF, Liu J, Zhang L, Jiang JY, Russell M, Lyeth BG, Nolta JA, Zhao M. Electrical Guidance of Human Stem Cells in the Rat Brain. *Stem Cell Reports.* 9:177-189, 2017.

Finnie JW, Blumbergs PC, Cai Z, Manavis J. Expression of the water channel protein, aquaporin-4, in mouse brains exposed to mobile telephone radiofrequency fields. *Pathology*. 41:473-475, 2009a.

Finnie JW, Chidlow G, Blumbergs PC, Manavis J, Cai Z. Heat shock protein induction in fetal mouse brain as a measure of stress after whole of gestation exposure to mobile telephony radiofrequency fields. *Pathology*. 41:276-279, 2009b.

Finnie JW, Cai Z, Manavis J, Helps S, Blumbergs PC. Microglial activation as a measure of stress in mouse brains exposed acutely (60 minutes) and long-term (2 years) to mobile telephone radiofrequency fields. *Pathology*. 42:151-154, 2010.

Fragopoulou AF, Miltiadous P, Stamatakis A, Stylianopoulou F, Koussoulakos SL, Margaritis LH. Whole body exposure with GSM 900-MHz affects spatial memory in mice. *Pathophysiology*. 17:179-187, 2010.

Fragopoulou AF, Samara A, Antonelou MH, Xanthopoulou A, Papadopoulou A, Vougas K, Koutsogiannopoulou E, Anastasiadou E, Stravopodis DJ, Tsangaris GT, Margaritis LH. Brain proteome response following whole body exposure of mice to mobile phone or wireless DECT base radiation. *Electromagn Biol Med*. 31:250-274, 2012.

Fritzer G, Göder R, Friege L, Wachter J, Hansen V, Hinze-Selch D, Aldenhoff JB. Effects of short- and long-term pulsed radiofrequency electromagnetic fields on night sleep and cognitive functions in healthy subjects. *Bioelectromagnetics*. 28:316-325, 2007.

Gandhi OP, Morgan LL, de Salles AA, Han YY, Herberman RB, Davis DL. Exposure limits: the underestimation of absorbed cell phone radiation, especially in children. *Electromagn. Biol. Med*. 31:34-51, 2012.

Gao X, Luo R, Ma B, Wang H, Liu T, Zhang J, Lian Z, Cui X. [Interference of vitamin E on the brain tissue damage by electromagnetic radiation of cell phone in pregnant and fetal rats]. *Wei Sheng Yan Jiu*. 42:642-646, 2013. [Article in Chinese]

Gevrek F. Histopathological, immunohistochemical, and stereological analysis of the effect of *Gingko biloba* (Egb761) on the hippocampus of rats exposed to long-term cellphone radiation. *Histol Histopathol*. 2017 Nov 9:11943.

Ghazizadeh V, Nazıroğlu M. Electromagnetic radiation (Wi-Fi) and epilepsy induce calcium entry and apoptosis through activation of TRPV1 channel in hippocampus and dorsal root ganglion of rats. *Metab Brain Dis*. 29:787-799, 2014.

Ghosn R, Yahia-Cherif L, Hugueville L, Ducorps A, Lemaréchal JD, Thuróczy G, de Seze R, Selmaoui B. Radiofrequency signal affects alpha band in resting electroencephalogram. *J Neurophysiol*. 113:2753-2759, 2015.

- Gökçek-Saraç Ç, Er H, Kencebay Manas C, Kantar Gok D, Özen Ş, Derin N. Effects of acute and chronic exposure to both 900 MHz and 2100 MHz electromagnetic radiation on glutamate receptor signaling pathway. *Int J Radiat Biol.* 93:980-989, 2017.
- Grafström G, Nittby H, Brun A, Malmgren L, Persson BR, Salford LG, Eberhardt J. Histopathological examinations of rat brains after long-term exposure to GSM-900 mobile phone radiation. *Brain Res Bull.* 77:257-263, 2008.
- Gupta N, Goyal D, Sharma R, Arora KS. Effect of prolonged use of mobile phone on brainstem auditory evoked potentials. *J Clin Diagn Res.* 9:CC07-9, 2015.
- Haarala C, Takio F, Rintee T, Laine M, Koivisto M, Revonsuo A, Hämäläinen H. Pulsed and continuous wave mobile phone exposure over left versus right hemisphere: effects on human cognitive function. *Bioelectromagnetics.* 28:289-295, 2007.
- Haghani M, Shabani M, Moazzami K. Maternal mobile phone exposure adversely affects the electrophysiological properties of Purkinje neurons in rat offspring. *Neuroscience.* 250:588-598, 2013.
- Hao Y, Yang X, Chen C, Yuan-Wang, Wang X, Li M, Yu Z. STAT3 signalling pathway is involved in the activation of microglia induced by 2.45 GHz electromagnetic fields. *Int J Radiat Biol.* 86:27-36, 2010.
- Hao D, Yang L, Chen S, Tong J, Tian Y, Su B, Wu S, Zeng Y. Effects of long-term electromagnetic field exposure on spatial learning and memory in rats. *Neurol Sci.* 34:157-164, 2013.
- Hareuveny R, Eliyahu I, Luria R, Meiran N, Margalioth M. Cognitive effects of cellular phones: a possible role of non-radiofrequency radiation factors. *Bioelectromagnetics.* 32:585-588, 2011.
- Hassanshahi A, Shafeie SA, Fatemi I, Hassanshahi E, Allahtavakoli M, Shabani M, Roohbakhsh A, Shamsizadeh A. The effect of Wi-Fi electromagnetic waves in unimodal and multimodal object recognition tasks in male rats. *Neurol Sci.* 38:1069-1076, 2017.
- He GL, Luo Z, Shen TT, Li P, Yang J, Luo X, Chen CH, Gao P, Yang XS. Inhibition of STAT3- and MAPK-dependent PGE2 synthesis ameliorates phagocytosis of fibrillar  $\beta$ -amyloid peptide (1-42) via EP2 receptor in EMF-stimulated N9 microglial cells. *J Neuroinflammation.* 13:296, 2016.
- Hidisoglu E, Kantar Gok D, Er H, Akpınar D, Uysal F, Akkoyunlu G, Ozen S, Agar A, Yargicoglu P. 2100-MHz electromagnetic fields have different effects on visual evoked potentials and oxidant/antioxidant status depending on exposure duration. *Brain Res.* 1635:1-11, 2016.
- Hirose H, Sasaki A, Ishii N, Sekijima M, Iyama T, Nojima T, Ugawa Y. 1950 MHz IMT-2000 field does not activate microglial cells in vitro. *Bioelectromagnetics.* 31:104-112, 2010.

Hountala CD, Maganioti AE, Papageorgiou CC, Nanou ED, Kyprianou MA, Tsiafakis VG, Rabavilas AD, Capsalis CN. The spectral power coherence of the EEG under different EMF conditions. *Neurosci Lett.* 441:188-192, 2008.

Hu S, Peng R, Wang C, Wang S, Gao Y, Dong J, Zhou H, Su Z, Qiao S, Zhang S, Wang L, Wen X. Neuroprotective effects of dietary supplement Kang-fu-ling against high-power microwave through antioxidant action. *Food Funct.* 5:2243-2251, 2014.

Hu Y, Lai J, Wan B, Liu X, Zhang Y, Zhang J, Sun D, Ruan G, Liu E, Liu GP, Chen C, Wang DW. Long-term exposure to ELF-MF ameliorates cognitive deficits and attenuates tau hyperphosphorylation in 3xTg AD mice. *Neurotoxicology.* 53:290-300, 2016.

Hung CS, Anderson C, Horne JA, McEvoy P. Mobile phone 'talk-mode' signal delays EEG-determined sleep onset. *Neurosci Lett.* 421:82-86, 2007.

İkinci A, Odacı E, Yıldırım M, Kaya H, Akça M, Hancı H, Aslan A, Sönmez OF, Baş O. The effects of prenatal exposure to a 900 megahertz electromagnetic field on hippocampus morphology and learning behavior in rat pups. *NeuroQuantology.* 11:582-590, 2013.

İkinci A, Mercantepe T, Unal D, Erol HS, Şahin A, Aslan A, Baş O, Erdem H, Sönmez OF, Kaya H, Odacı E. Morphological and antioxidant impairments in the spinal cord of male offspring rats following exposure to a continuous 900MHz electromagnetic field during early and mid-adolescence. *J Chem Neuroanat.* 75(Pt B):99-104, 2016.

Imge EB, Kiliçoğlu B, Devrim E, Cetin R, Durak I. Effects of mobile phone use on brain tissue from the rat and a possible protective role of vitamin C - a preliminary study. *Int J Radiat Biol.* 86:1044-1049, 2010.

Inomata-Terada S, Okabe S, Arai N, Hanajima R, Terao Y, Frubayashi T, Ugawa Y. Effects of high frequency electromagnetic field (EMF) emitted by mobile phones on the human motor cortex. *Bioelectromagnetics.* 28:553-561, 2007.

Irlenbusch L, Bartsch B, Cooper J, Herget I, Marx B, Raczek J, Thoss F. Influence of a 902.4 MHz GSM signal on the human visual system: investigation of the discrimination threshold. *Bioelectromagnetics.* 28:648-654, 2007.

Jing J, Yuhua Z, Xiao-qian Y, Rongping J, Dong-mei G, Xi C. The influence of microwave radiation from cellular phone on fetal rat brain. *Electromagn Biol Med.* 31:57-66, 2012.

Jorge-Mora T, Köktürk S, Yardimoglu M, Celikozlu SD, Dolanbay EG, Cimbiz A. Effect of *Lycopersicon esculentum* extract on apoptosis in the rat cerebellum, following prenatal and postnatal exposure to an electromagnetic field. *Exp Ther Med.* 6:52-56, 2013.

Júnior LC, Guimarães ED, Musso CM, Stabler CT, Garcia RM, Mourão-Júnior CA, Andreazzi AE. Behavior and memory evaluation of Wistar rats exposed to 1.8 GHz radiofrequency electromagnetic radiation. *Neurol Res.* 36:800-803, 2014.

Kang KA, Lee HC, Lee JJ, Hong MN, Park MJ, Lee YS, Choi HD, Kim N, Ko YK, Lee JS. Effects of combined radiofrequency radiation exposure on levels of reactive oxygen species in neuronal cells. *J Radiat Res.* 55:265-276, 2014.

Kaprana AE, Chimona TS, Papadakis CE, Velegrakis SG, Vardiambasis IO, Adamidis G, Velegrakis GA. Auditory brainstem response changes during exposure to GSM-900 radiation: an experimental study. *Audiol Neurotol.* 16:270-276, 2011.

Kerimoğlu G, Aslan A, Baş O, Çolakoğlu S, Odacı E. Adverse effects in lumbar spinal cord morphology and tissue biochemistry in Sprague Dawley male rats following exposure to a continuous 1-h a day 900-MHz electromagnetic field throughout adolescence. *J Chem Neuroanat.* 78:125-130, 2016a.

Kerimoğlu G, Hancı H, Baş O, Aslan A, Erol HS, Turgut A, Kaya H, Çankaya S, Sönmez OF, Odacı E. Pernicious effects of long-term, continuous 900-MHz electromagnetic field throughout adolescence on hippocampus morphology, biochemistry and pyramidal neuron numbers in 60-day-old Sprague Dawley male rats. *J Chem Neuroanat.* 77:169-175, 2016b.

Kesari KK, Kumar S, Behari J. 900-MHz microwave radiation promotes oxidation in rat brain. *Electromagn Biol Med.* 30:219-234, 2011.

Khullar S, Sood A, Sood S. Auditory brainstem responses and EMFs generated by mobile phones. *Indian J Otolaryngol Head Neck Surg.* 65(Suppl 3):645-649, 2013.

Kim HJ, Jung J, Park JH, Kim JH, Ko KN, Kim CW. Extremely low-frequency electromagnetic fields induce neural differentiation in bone marrow derived mesenchymal stem cells. *Exp Biol Med* (Maywood). 238:923-931, 2013.

Kim JH, Yu DH, Huh YH, Lee EH, Kim HG, Kim HR. Long-term exposure to 835 MHz RF-EMF induces hyperactivity, autophagy and demyelination in the cortical neurons of mice. *Sci Rep.* 7:41129, 2017a.

Kim JH, Yu DH, Kim HJ, Huh YH, Cho SW, Lee JK, Kim HG, Kim HR. Exposure to 835 MHz radiofrequency electromagnetic field induces autophagy in hippocampus but not in brain stem of mice. *Toxicol Ind Health.* 2017b Jan 1:748233717740066. doi: 10.1177/0748233717740066.

Kim JY, Kim HJ, Kim N, Kwon JH, Park MJ. Effects of radiofrequency field exposure on glutamate-induced oxidative stress in mouse hippocampal HT22 cells. *Int J Radiat Biol.* 93:249-256, 2017.



- Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. Effects of weak mobile phone - electromagnetic fields (GSM, UMTS) on well-being and resting EEG. *Bioelectromagnetics*. 29:479-487, 2008a.
- Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. Effects of weak mobile phone - electromagnetic fields (GSM, UMTS) on event related potentials and cognitive functions. *Bioelectromagnetics*. 29:488-497, 2008b.
- Klose M, Grote K, Spathmann O, Streckert J, Clemens M, Hansen VW, Lerchl A. Effects of early-onset radiofrequency electromagnetic field exposure (GSM 900 MHz) on behavior and memory in rats. *Radiat Res*. 182:435-447, 2014.
- Köktürk S, Yardimoglu M, Celikozlu SD, Dolanbay EG, Cimbiz A. Effect of *Lycopersicon esculentum* extract on apoptosis in the rat cerebellum, following prenatal and postnatal exposure to an electromagnetic field. *Exp Ther Med*. 6:52-56, 2013.
- Krause CM, Pesonen M, Haarala Björnberg C, Hämäläinen H. Effects of pulsed and continuous wave 902 MHz mobile phone exposure on brain oscillatory activity during cognitive processing. *Bioelectromagnetics*. 28:296-308, 2007.
- Kumar RS, Sareesh NN, Nayak S, Mailankot M. Hypoactivity of Wistar rats exposed to mobile phone on elevated plus maze. *Indian J Physiol Pharmacol*. 53:283-286, 2009.
- Kumari K, Koivisto H, Viluksela M, Paldanius KMA, Marttinen M, Hiltunen M, Naarala J, Tanila H, Juutilainen J. Behavioral testing of mice exposed to intermediate frequency magnetic fields indicates mild memory impairment. *PLoS One*. 2017 Dec 4;12(12):e0188880.
- Kumlin T, Iivonen H, Miettinen P, Juvonen A, van Groen T, Puranen L, Pitkäaho R, Juutilainen J, Tanila H. Mobile phone radiation and the developing brain: behavioral and morphological effects in juvenile rats. *Radiat Res*. 168:471-479, 2007.
- Kwon MS, Kujala T, Huotilainen M, Shestakova A, Näätänen R, Hämäläinen H. Pre-attentive auditory information processing under exposure to the 902 MHz GSM mobile phone electromagnetic field: a mismatch negativity (MMN) study. *Bioelectromagnetics*. 30:241-248, 2009.
- Kwon MS, Jääskeläinen SK, Toivo T, Hämäläinen H. No effects of mobile phone electromagnetic field on auditory brainstem response. *Bioelectromagnetics*. 31:48-55, 2010a.
- Kwon MS, Huotilainen M, Shestakova A, Kujala T, Näätänen R, Hämäläinen H. No effects of mobile phone use on cortical auditory change-detection in children: an ERP study. *Bioelectromagnetics*. 31:191-199, 2010b.
- Lahham A, Hammash A. Outdoor radiofrequency radiation levels in the West Bank-Palestine. *Radiat Prot Dosimetry*. 149:399-402, 2012.

- Lai H. Neurological effects of microwave irradiation. In "Advances in Electromagnetic Fields in Living Systems, Vol. 1", Lin JC (ed.), Plenum Press, New York, 1994, pp. 27-80.
- Lai H, Singh NP. Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. *Bioelectromagnetics*. 16:207-210, 1995.
- Lai H, Horita A, Chou CK, Guy AW. Low-level microwave irradiation affects central cholinergic activity in the rat. *J Neurochem*. 48:40-45, 1987.
- Landler L, Painter MS, Youmans PW, Hopkins WA, Phillips JB. Spontaneous magnetic alignment by yearling snapping turtles: rapid association of radio frequency dependent pattern of magnetic input with novel surroundings. *PLoS One*. 10(5):e0124728, 2015.
- Lee D, Lee J, Lee I. Cell phone generated radio frequency electromagnetic field effects on the locomotor behaviors of the fishes *Poecilia reticulata* and *Danio rerio*. *Int J Radiat Biol*. 91:845-850, 2015.
- Lee W and Yang K-L. Using medaka embryos as a model system to study biological effects of the electromagnetic fields on development and behavior. *Ecotoxicol Environ Safety* 108:187-194, 2014.
- Leung S, Croft RJ, McKenzie RJ, Iskra S, Silber B, Cooper NR, O'Neill B, Cropley V, Diaz-Trujillo A, Hamblin D, Simpson D. Effects of 2G and 3G mobile phones on performance and electrophysiology in adolescents, young adults and older adults. *Clin Neurophysiol*. 122:2203-2216, 2011.
- Levitt, B.B. and Lai, H. Biological effects from exposure to electromagnetic radiation emitted by cell tower base stations and other antenna arrays. *Environ Rev*. 18:369-395, 2010.
- Li H, Peng R, Wang C, Qiao S, Yong-Zou, Gao Y, Xu X, Wang S, Dong J, Zuo H, Li-Zhao, Zhou H, Wang L, Hu X. Alterations of cognitive function and 5-HT system in rats after long term microwave exposure. *Physiol Behav*. 40:236-246, 2015.
- Li Y, Shi C, Lu G, Xu Q, Liu S. Effects of electromagnetic radiation on spatial memory and synapses in rat hippocampal CA1. *Neural Regen Res*. 7:1248-1255, 2012.
- Liu ML, Wen JQ, Fan YB. Potential protection of green tea polyphenols against 1800 MHz electromagnetic radiation-induced injury on rat cortical neurons. *Neurotox Res*. 20:270-276, 2011.
- Liu YX, Tai JL, Li GQ, Zhang ZW, Xue JH, Liu HS, Zhu H, Cheng JD, Liu YL, Li AM, Zhang Y. Exposure to 1950-MHz TD-SCDMA electromagnetic fields affects the apoptosis of astrocytes via caspase-3-dependent pathway. *PLoS One*. 7:e42332, 2012.
- López-Martín E, Bregains J, Relova-Quinteiro JL, Cadarso-Suárez C, Jorge-Barreiro FJ, Ares-Pena FJ. The action of pulse-modulated GSM radiation increases regional changes in brain activity

and c-Fos expression in cortical and subcortical areas in a rat model of picrotoxin-induced seizure proneness. *J Neurosci Res.* 87:1484-1499, 2009.

Loughran SP, McKenzie RJ, Jackson ML, Howard ME, Croft RJ. Individual differences in the effects of mobile phone exposure on human sleep: rethinking the problem. *Bioelectromagnetics.* 33:86-93, 2012.

Loughran SP, Benz DC, Schmid MR, Murbach M, Kuster N, Achermann P. No increased sensitivity in brain activity of adolescents exposed to mobile phone-like emissions. *Clin Neurophysiol.* 124:1303-1308, 2013.

Lowden A, Akerstedt T, Ingre M, Wiholm C, Hillert L, Kuster N, Nilsson JP, Arnetz B. Sleep after mobile phone exposure in subjects with mobile phone-related symptoms. *Bioelectromagnetics.* 32:4-14, 2011.

Lu Y, Xu S, He M, Chen C, Zhang L, Liu C, Chu F, Yu Z, Zhou Z, Zhong M. Glucose administration attenuates spatial memory deficits induced by chronic low-power-density microwave exposure. *Physiol Behav.* 106:631-637, 2012.

Lu Y, He M, Zhang Y, Xu S, Zhang L, He Y, Chen C, Liu C, Pi H, Yu Z, Zhou Z. Differential pro-inflammatory responses of astrocytes and microglia involve STAT3 activation in response to 1800 MHz radiofrequency fields. *PLoS One.* 9:e108318, 2014.

Luria R, Eliyahu I, Hareuveny R, Margaliot M, Meiran N. Cognitive effects of radiation emitted by cellular phones: the influence of exposure side and time. *Bioelectromagnetics.* 30:198-204, 2009.

Lustenberger C, Murbach M, Durr R, Schmid MR, Kuster N, Achermann P, Huber R. Stimulation of the brain with radiofrequency electromagnetic field pulses affects sleep-dependent performance improvement. *Brain Stimul.* 6:805-811, 2013.

Lustenberger, C., Murbach, M., Tüshaus, L., Wehrle, F., Kuster, N., Achermann, P. and Huber, R., Inter-individual and intra-individual variation of the effects of pulsed RF EMF exposure on the human sleep EEG. *Bioelectromagnetics.* 36: 169-177, 2015.

Lv B, Chen Z, Wu T, Shao Q, Yan D, Ma L, Lu K, Xie Y. The alteration of spontaneous low frequency oscillations caused by acute electromagnetic fields exposure. *Clin Neurophysiol.* 125:277-286, 2014a.

Lv B, Su C, Yang L, Xie Y, Wu T. Whole brain EEG synchronization likelihood modulated by long term evolution electromagnetic fields exposure. *Conf Proc IEEE Eng Med Biol Soc.* 2014:986-989, 2014b.

Maaroufi K, Had-Aissouni L, Melon C, Sakly M, Abdelmelek H, Poucet B, Save E. Spatial learning, monoamines and oxidative stress in rats exposed to 900MHz electromagnetic field in combination with iron overload. *Behav Brain Res.* 258:80-89, 2014.

Maganioti AE, Hountala CD, Papageorgiou CC, Kyprianou MA, Rabavilas AD, Capsalis CN. Principal component analysis of the P600 waveform: RF and gender effects. *Neurosci Lett.* 478:19-23, 2010.

Malek F, Rani KA, Rahim HA, Omar MH. Effect of short-term mobile phone base station exposure on cognitive performance, body temperature, heart rate and blood pressure of Malaysians. *Sci Rep.* 5:13206, 2015.

Malkemper EP, Eder SH, Begall S, Phillips JB, Winklhofer M, Hart V, Burda H. Magnetoreception in the wood mouse (*Apodemus sylvaticus*): influence of weak frequency-modulated radio frequency fields. *Sci Rep.* 29;4:9917, 2015.

Mandalà M, Colletti V, Sacchetto L, Manganotti P, Ramat S, Marcocci A, Colletti L. Effect of Bluetooth headset and mobile phone electromagnetic fields on the human auditory nerve. *Laryngoscope.* 124:255-259, 2014.

Maskey D, Kim M, Aryal B, Pradhan J, Choi IY, Park KS, Son T, Hong SY, Kim SB, Kim HG, Kim MJ. Effect of 835 MHz radiofrequency radiation exposure on calcium binding proteins in the hippocampus of the mouse brain. *Brain Res.* 1313:232-241, 2010a.

Maskey D, Pradhan J, Aryal B, Lee CM, Choi IY, Park KS, Kim SB, Kim HG, Kim MJ. Chronic 835-MHz radiofrequency exposure to mice hippocampus alters the distribution of calbindin and GFAP immunoreactivity. *Brain Res.* 1346:237-246, 2010b.

Maskey D, Kim HJ, Kim HG, Kim MJ. Calcium-binding proteins and GFAP immunoreactivity alterations in murine hippocampus after 1 month of exposure to 835 MHz radiofrequency at SAR values of 1.6 and 4.0 W/kg. *Neurosci Lett.* 506:292-296, 2012.

Maskey D, Kim MJ. Immunohistochemical localization of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor in the superior olivary complex of mice after radiofrequency exposure. *Neuroscience Letters.* 564:78-82, 2014.

Masuda H, Ushiyama A, Takahashi M, Wang J, Fujiwara O, Hikage T, Nojima T, Fujita K, Kudo M, Ohkubo C. Effects of 915 MHz electromagnetic-field radiation in TEM cell on the blood-brain barrier and neurons in the rat brain. *Radiat Res.* 172:66-73, 2009.

Mathur R. Effect of chronic intermittent exposure to AM radiofrequency field on responses to various types of noxious stimuli in growing rats. *Electromagn Biol Med.* 27:266-276, 2008.

Megha K, Deshmukh PS, Banerjee BD, Tripathi AK, Abegaonkar MP. Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats. *Indian J Exp Biol.* 50:889-896, 2012.

Megha K, Deshmukh PS, Ravi AK, Tripathi AK, Abegaonkar MP, Banerjee BD. Effect of low-intensity microwave radiation on monoamine neurotransmitters and their key regulating enzymes in rat brain. *Cell Biochem Biophys.* 73:93-100, 2015.

Meral I, Mert H, Mert N, Deger Y, Yoruk I, Yetkin A, Keskin S. Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs. *Brain Res.* 1169:120-124, 2007.

Mild KH, Andersen JB, Pedersen GF. Is there any exposure from a mobile phone in stand-by mode? *Electromagn Biol Med.* 31:52-56, 2012.

Mohler E, Frei P, Braun-Fahrlander C, Fröhlich J, Neubauer G, Rösli M; Qualifex Team. Effects of everyday radiofrequency electromagnetic-field exposure on sleep quality: a cross-sectional study. *Radiat Res.* 174:347-356, 2010.

Mohler E, Frei P, Fröhlich J, Braun-Fahrlander C, Rösli M; QUALIFEX-team. Exposure to radiofrequency electromagnetic fields and sleep quality: a prospective cohort study. *PLoS One.* 7:e37455, 2012.

Mohammed HS, Fahmy HM, Radwah NM, Elsayed AA. Non-thermal continuous and modulated electromagnetic radiation fields effects on sleep EEG of rats. *J Adv Res.* 4: 81-187, 2013.

Mortazavi SM, Rouintan MS, Taeb S, Dehghan N, Ghaffarpanah AA, Sadeghi Z, Ghafouri F. Human short-term exposure to electromagnetic fields emitted by mobile phones decreases computer-assisted visual reaction time. *Acta Neurol Belg.* 112:171-175, 2012.

Mortazavi SM, Taeb S, Dehghan N. Alterations of visual reaction time and short term memory in military radar personnel. *Iran J Public Health.* 42:428-435, 2013.

Motawi TK, Darwish HA, Moustafa YM, Labib MM. Biochemical modifications and neuronal damage in brain of young and adult rats after long-term exposure to mobile phone radiations. *Cell Biochem Biophys.* 70:845-855, 2014.

Movvahedi MM, Tavakkoli-Golpayegani A, Mortazavi SA, Haghani M, Razi Z, Shojaie-Fard MB, Zare M, Mina E, Mansourabadi L, Nazari-Jahromi, Safari A, Shokrpour N, Mortazavi SM. Does exposure to GSM 900 MHz mobile phone radiation affect short-term memory of elementary school students? *J Pediatr Neurosci.* 9:121-124, 2014.

Mugunthan N, Shanmugasamy K, Anbalagan J, Rajanarayanan S, Meenachi S. Effects of long term exposure of 900-1800 MHz radiation emitted from 2G mobile phone on mice hippocampus- A histomorphometric study. *J Clin Diagn Res.* 10:AF01-6, 2016.

- Nakatani-Enomoto S, Furubayashi T, Ushiyama A, Groiss SJ, Ueshima K, Sokejima S, Simba AY, Wake K, Watanabe SI, Nishikawa M, Miyawaki K, Taki M, Ugawa Y. Effects of electromagnetic fields emitted from W-CDMA-like mobile phones on sleep in humans. *Bioelectromagnetics*. 34:589-598, 2013.
- Narayanan SN, Kumar RS, Potu BK, Nayak S, Mailankot M. Spatial memory performance of Wistar rats exposed to mobile phone. *Clinics (Sao Paulo)*. 64:231-234, 2009.
- Narayanan SN, Kumar RS, Potu BK, Nayak S, Bhat PG, Mailankot M. Effect of radio-frequency electromagnetic radiations (RF-EMR) on passive avoidance behaviour and hippocampal morphology in Wistar rats. *Ups J Med Sci*. 115:91-96, 2010.
- Narayanan SN, Kumar RS, Paval J, Kedage V, Bhat MS, Nayak S, Bhat PG. Analysis of emotionality and locomotion in radio-frequency electromagnetic radiation exposed rats. *Neurol Sci*. 34:1117-1124, 2013.
- Narayanan SN, Kumar RS, Kedage V, Nalini K, Nayak S, Bhat PG. Evaluation of oxidant stress and antioxidant defense in discrete brain regions of rats exposed to 900 MHz radiation. *Bratisl Lek Listy*. 115:260-266, 2014.
- Narayanan SN, Kumar RS, Karun KM, Nayak SB, Bhat PG. Possible cause for altered spatial cognition of prepubescent rats exposed to chronic radiofrequency electromagnetic radiation. *Metab Brain Dis*. 30:1193-1206, 2015.
- Naziroğlu M, Gümral N. Modulator effects of L-carnitine and selenium on wireless devices (2.45 GHz)-induced oxidative stress and electroencephalography records in brain of rat. *Int J Radiat Biol*. 85:680-689, 2009.
- Naziroğlu M, Çelik Ö, Özgül C, Çiğ B, Doğan S, Bal R, Gümral N, Rodríguez AB, Pariente JA. Melatonin modulates wireless (2.45 GHz)-induced oxidative injury through TRPM2 and voltage gated Ca(2+) channels in brain and dorsal root ganglion in rat. *Physiol Behav*. 105:683-692, 2012.
- Ning W, Xu SJ, Chiang H, Xu ZP, Zhou SY, Yang W, Luo JH. Effects of GSM 1800 MHz on dendritic development of cultured hippocampal neurons. *Acta Pharmacol Sin*. 28:1873-1880, 2007.
- Nirwane A, Sridhar V, Majumdar A. Neurobehavioural changes and brain oxidative stress induced by acute exposure to GSM 900 mobile phone radiations in Zebrafish (*Danio rerio*). *Toxicol Res*. 32:123-132, 2016.
- Nittby H, Widegren B, Krogh M, Grafström G, Berlin H, Rehn G, Eberhardt JL, Malmgren L, Persson BRR, Salford L. Exposure to radiation from global system for mobile communications at 1,800 MHz significantly changes gene expression in rat hippocampus and cortex. *Environmentalist*. 28:458-465, 2008.

- Nittby H, Grafström G, Tian DP, Malmgren L, Brun A, Persson BR, Salford LG, Eberhardt J. Cognitive impairment in rats after long-term exposure to GSM-900 mobile phone radiation. *Bioelectromagnetics*. 29:219-232, 2008.
- Nittby H, Brun A, Eberhardt J, Malmgren L, Persson BR, Salford LG. Increased blood-brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. *Pathophysiology*. 16:103-112, 2009.
- Noor NA, Mohammed HS, Ahmed NA, Radwan NM. Variations in amino acid neurotransmitters in some brain areas of adult and young male albino rats due to exposure to mobile phone radiation. *Eur Rev Med Pharmacol Sci*. 15:729-742, 2011
- Ntzouni MP, Stamatakis A, Stylianopoulou F, Margaritis LH. Short-term memory in mice is affected by mobile phone radiation. *Pathophysiology*. 18:193-199, 2011.
- Ntzouni MP, Skouroliahou A, Kostomitsopoulos N, Margaritis LH. Transient and cumulative memory impairments induced by GSM 1.8 GHz cell phone signal in a mouse model. *Electromagn Biol Med*. 32:95-120, 2013
- Nylund R, Kuster N, Leszczynski D. Analysis of proteome response to the mobile phone radiation in two types of human primary endothelial cells. *Proteome Sci*. 8:52, 2010.
- Odaci E, Bas O, Kaplan S. Effects of prenatal exposure to a 900 MHz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study. *Brain Res*. 1238:224-229, 2008.
- Odacı E, İkinci A, Yıldırım M, Kaya H, Akça M, Hancı H, Sönmez OF, Aslan A, Okuyan M, Baş O. The effects of 900 megahertz electromagnetic field applied in the prenatal period on spinal cord morphology and motor behavior in female rat pups. *NeuroQuantology* 11:573-581, 2013.
- Odacı E, Hancı H, İkinci A, Sönmez OF, Aslan A, Şahin A, Kaya H, Çolakoğlu S, Baş O. Maternal exposure to a continuous 900-MHz electromagnetic field provokes neuronal loss and pathological changes in cerebellum of 32-day-old female rat offspring. *J Chem Neuroanat*. 75(Pt B):105-110, 2016.
- Othman H, Ammari M, Sakly M, Abdelmelek H. Effects of prenatal exposure to WIFI signal (2.45GHz) on postnatal development and behavior in rat: Influence of maternal restraint. *Behav Brain Res*. 326:291-302, 2017.
- Özgür A, Tümkaya L, Terzi S, Kalkan Y, Erdivanlı ÖÇ, Dursun E. Effects of chronic exposure to electromagnetic waves on the auditory system. *Acta Otolaryngol*. 135:765-770, 2015.
- Pakhomov A, Bojarinova J, Cherbunin R, Chetverikova R, Grigoryev PS, Kavokin K, Kobylkov D, Lubkovskaja R, Chernetsov N. Very weak oscillating magnetic field disrupts the magnetic

compass of songbird migrants. *J R Soc Interface*. 2017 Aug;14(133). pii: 20170364. doi: 10.1098/rsif.2017.0364.

Panda NK, Jain R, Bakshi J, Munjal S. Audiologic disturbances in long-term mobile phone users. *J Otolaryngol Head Neck Surg*. 39:5-11, 2010.

Panda NK, Modi R, Munjal S, Virk RS. Auditory changes in mobile users: is evidence forthcoming? *Otolaryngol Head Neck Surg*. 144:581-585, 2011.

Parazzini M, Sibella F, Lutman ME, Mishra S, Moulin A, Sliwinska-Kowalska M, Woznicka E, Politanski P, Zmyslony M, Thuroczy G, Molnár F, Kubinyi G, Tavartkiladze G, Bronyakin S, Uloziene I, Uloza V, Gradauskiene E, Ravazzani P. Effects of UMTS cellular phones on human hearing: results of the European project EMFnEAR. *Radiat Res*. 172:244-251, 2009.

Pelletier A, Delanaud S, Décima P, Thuroczy G, de Seze R, Cerri M, Bach V, Libert JP, Loos N. Effects of chronic exposure to radiofrequency electromagnetic fields on energy balance in developing rats. *Environ Sci Pollut Res Int*. 20:2735-2746, 2013.

Pelletier A, Delanaud S, de Seze R, Bach V, Libert JP, Loos N. Does exposure to a radiofrequency electromagnetic field modify thermal preference in juvenile rats? *PLoS One*. 9:e99007, 2014.

Perentos N, Croft RJ, McKenzie RJ, Cvetkovic D, Cosic I. Comparison of the effects of continuous and pulsed mobile phone like RF exposure on the human EEG. *Australas Phys Eng Sci Med*. 30:274-280, 2007.

Perentos N, Croft RJ, McKenzie RJ, Cvetkovic D, Cosic I. The effect of GSM-like ELF radiation on the alpha band of the human resting EEG. *Conf Proc IEEE Eng Med Biol Soc*. 2008:5680-5683, 2008.

Perentos N, Croft RJ, McKenzie RJ, Cosic I. The alpha band of the resting electroencephalogram under pulsed and continuous radio frequency exposures. *IEEE Trans Biomed Eng*. 60:1702-1710, 2013.

Poullétier de Gannes F, Haro E, Hurtier A, Taxile M, Ruffié G, Billaudel B, Veyret B, Lagroye I. Effect of exposure to the edge signal on oxidative stress in brain cell models. *Radiat Res*. 175:225-230, 2011.

Poullétier de Gannes F, Masuda H, Billaudel B, Poque-Haro E, Hurtier A, Lévêque P, Ruffié G, Taxile M, Veyret B, Lagroye I. Effects of GSM and UMTS mobile telephony signals on neuron degeneration and blood-brain barrier permeation in the rat brain. *Sci Rep*. 2017 Nov 14;7(1):15496. doi: 10.1038/s41598-017-15690-1.

Qiao S, Peng R, Yan H, Gao Y, Wang C, Wang S, Zou Y, Xu X, Zhao L, Dong J, Su Z, Feng X, Wang L, Hu X. Reduction of Phosphorylated Synapsin I (Ser-553) Leads to spatial memory impairment by attenuating GABA release after microwave exposure in Wistar Rats. *PLoS One*. 9:e95503, 2014.



Qin F, Yuan H, Nie J, Cao Y, Tong J. [Effects of nano-selenium on cognition performance of mice exposed in 1800 MHz radiofrequency fields]. *Wei Sheng Yan Jiu*. 43:16-21, 2014. [Article in Chinese]

Rağbetli MC, Aydinlioğlu A, Koyun N, Rağbetli C, Karayel M. Effect of prenatal exposure to mobile phone on pyramidal cell numbers in the mouse hippocampus: a stereological study. *Int J Neurosci*. 119:1031-1041, 2009.

Rağbetli MC, Aydinlioğlu A, Koyun N, Rağbetli C, Bektas S, Ozdemir S. The effect of mobile phone on the number of Purkinje cells: a stereological study. *Int J Radiat Biol*. 86:548-554, 2010.

Razavinasab M, Moazzami K, Shabani M. Maternal mobile phone exposure alters intrinsic electrophysiological properties of CA1 pyramidal neurons in rat offspring. *Toxicol Ind Health*. 32:968-979, 2016.

Redmayne M, Smith E, and Abramson MJ. The relationship between adolescents' well-being and their wireless phone use: a cross-sectional study. *Environ Health*. 12:90, 2013.

Redmayne M, Smith CL, Benke G, Croft RJ, Dalecki A, Dimitriadis C, Kaufman J, Macleod S, Sim MR, Wolfe R, Abramson MJ. Use of mobile and cordless phones and cognition in Australian primary school children: a prospective cohort study. *Environ Health*. 15:26, 2016.

Regel SJ, Tinguely G, Schuderer J, Adam M, Kuster N, Landolt HP, Achermann P. Pulsed radio-frequency electromagnetic fields: dose-dependent effects on sleep, the sleep EEG and cognitive performance. *J Sleep Res*. 16:253-258, 2007.

Riddervold IS, Pedersen GF, Andersen NT, Pedersen AD, Andersen JB, Zachariae R, Møhlhave L, Sigsgaard T, Kjaergaard SK. Cognitive function and symptoms in adults and adolescents in relation to rf radiation from UMTS base stations. *Bioelectromagnetics*. 29:257-267, 2008.

Roggeveen S, van Os J, Viechtbauer W, Lousberg R. EEG changes due to experimentally induced 3G mobile phone radiation. *PLoS One*. 10:e0129496, 2015a.

Roggeveen S, van Os J, Lousberg R. Does the brain detect 3G mobile phone radiation peaks? An explorative in-depth analysis of an experimental study. *PLoS One*. 10:e0125390, 2015b.

Roser K, Schoeni A, Rösli M. Mobile phone use, behavioural problems and concentration capacity in adolescents: A prospective study. *Int J Hyg Environ Health*. 219:759-769, 2016.

Şahin A, Aslan A, Baş O, İkinci A, Özyılmaz C, Fikret Sönmez O, Çolakoğlu S, Odacı E. Deleterious impacts of a 900MHz electromagnetic field on hippocampal pyramidal neurons of 8-week-old Sprague Dawley male rats. *Brain Res*. 1624:232-238, 2015.

Saikhedkar N, Bhatnagar M, Jain A, Sukhwai P, Sharma C, Jaiswal N. Effects of mobile phone radiation (900 MHz radiofrequency) on structure and functions of rat brain. *Neurol Res.* 36:1072-1076, 2014.

Salford LG, Brun AE, Eberhardt JL, Malmgren L, Persson BR. Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones. *Environ Health Perspect.* 111:881-883, 2003.

Salunke BP, Umathe SN, Chavan JG. Behavioral in-effectiveness of high frequency electromagnetic field in mice. *Physiol Behav.* 140:32-37, 2015.

Sarapultseva EI, Igolkina JV, Tikhonov VN, Dubrova YE. The in vivo effects of low-intensity radiofrequency fields on the motor activity of protozoa. *Int J Radiat Biol.* 90:262-267, 2014.

Sauter C, Dorn H, Bahr A, Hansen ML, Peter A, Bajbouj M, Danker-Hopfe H. Effects of exposure to electromagnetic fields emitted by GSM 900 and WCDMA mobile phones on cognitive function in young male subjects. *Bioelectromagnetics.* 32:179-190, 2011.

Sauter C, Eggert T, Dorn H, Schmid G, Bolz T, Marasanov A, Hansen ML, Peter A, Danker-Hopfe H. Do signals of a hand-held TETRA transmitter affect cognitive performance, well-being, mood or somatic complaints in healthy young men? Results of a randomized double-blind cross-over provocation study. *Environ Res.* 140:85-94, 2015.

Schmid MR, Loughran SP, Regel SJ, Murbach M, Bratic Grunauer A, Rusterholz T, Bersagliere A, Kuster N, Achermann P. Sleep EEG alterations: effects of different pulse-modulated radio frequency electromagnetic fields. *J Sleep Res.* 21:50-58, 2012a.

Schmid MR, Murbach M, Lustenberger C, Maire M, Kuster N, Achermann P, Loughran SP. Sleep EEG alterations: effects of pulsed magnetic fields versus pulse-modulated radio frequency electromagnetic fields. *J Sleep Res.* 21:620-629, 2012b.

Schneider J, Stangassinger M. Nonthermal effects of lifelong high-frequency electromagnetic field exposure on social memory performance in rats. *Behav Neurosci.* 128:633-637, 2014.

Schoeni A, Roser K, Rösli M. Memory performance, wireless communication and exposure to radiofrequency electromagnetic fields: A prospective cohort study in adolescents. *Environ Int.* 85:343-351, 2015.

Schwarze S, Schneider NL, Reichl T, Dreyer D, Lefeldt N, Engels S, Baker N, Hore PJ, Mouritsen H. Weak broadband electromagnetic fields are more disruptive to magnetic compass orientation in a night-migratory songbird (*Erithacus rubecula*) than strong narrow-band fields. *Front Behav Neurosci.* 10:55, 2016.

Seckin E, Suren Basar F, Atmaca S, Kaymaz FF, Suzer A, Akar A, Sunan E, Koyuncu M. The effect

of radiofrequency radiation generated by a Global System for Mobile Communications source on cochlear development in a rat model. *J Laryngol Otol.* 128:400-405, 2014.

Sharma A, Sisodia R, Bhatnagar D, Saxena VK. Spatial memory and learning performance and its relationship to protein synthesis of Swiss albino mice exposed to 10 GHz microwaves. *Int J Radiat Biol.* 90:29-35, 2014.

Sharma A, Kesari KK, Saxena VK, Sisodia R. Ten gigahertz microwave radiation impairs spatial memory, enzymes activity, and histopathology of developing mice brain. *Mol Cell Biochem.* 435:1-13, 2017.

Shehu A, Mohammed A, Magaji RA, Muhammad MS. Exposure to mobile phone electromagnetic field radiation, ringtone and vibration affects anxiety-like behaviour and oxidative stress biomarkers in albino Wistar rats. *Metab Brain Dis.* 31:355-362, 2016.

Shirai T, Imai N, Wang J, Takahashi S, Kawabe M, Wake K, Kawai H, Watanabe S-I, Furukawa F, Fujiwara O. Multigenerational effects of whole body exposure to 2.14 GHz W-CDMA cellular phone signals on brain function in rats. *Bioelectromagnetics.* 35:497-511, 2014.

Sirav B, Seyhan N. Blood-brain barrier disruption by continuous-wave radio frequency radiation. *Electromagn Biol Med.* 28:215-222, 2009.

Sirav B, Seyhan N. Effects of radiofrequency radiation exposure on blood-brain barrier permeability in male and female rats. *Electromagn Biol Med.* 30:253-260, 2011.

Sirav B, Seyhan N. Effects of GSM modulated radio-frequency electromagnetic radiation on permeability of blood-brain barrier in male & female rats. *J Chem Neuroanat.* 75(Pt B):123-127, 2016.

Söderqvist F, Carlberg M, Hardell L. Mobile and cordless telephones, serum transthyretin and the blood-cerebrospinal fluid barrier: a cross-sectional study. *Environ Health.* 21; 8:19, 2009a.

Söderqvist F, Carlberg M, Hansson Mild K, Hardell L. Exposure to an 890-MHz mobile phone-like signal and serum levels of S100B and transthyretin in volunteers. *Toxicol Lett.* 189:63-66, 2009b.

Söderqvist F, Carlberg M, Hardell L. Use of wireless telephones and serum S100B levels: a descriptive cross-sectional study among healthy Swedish adults aged 18-65 years. *Sci Total Environ.* 407:798-805, 2009c.

Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, Krstic D, Cvetkovic T, Pavlovic V. Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. *J Radiat Res.* 49:579-586, 2008.

Sokolovic D, Djordjevic B, Kocic G, Babovic P, Ristic G, Stanojkovic Z, Sokolovic DM, Veljkovic A, Jankovic A, Radovanovic Z. The effect of melatonin on body mass and behaviour of rats during an exposure to microwave radiation from mobile phone. *Bratisl Lek Listy*. 113:265-269, 2012.

Son Y, Jeong YJ, Kwon JH, Choi HD, Pack JK, Kim N, Lee YS, Lee HJ. 1950 MHz radiofrequency electromagnetic fields do not aggravate memory deficits in 5xFAD mice. *Bioelectromagnetics*. 37(6):391-399, 2016.

Stefanics G, Kellényi L, Molnár F, Kubinyi G, Thuróczy G, Hernádi I. Short GSM mobile phone exposure does not alter human auditory brainstem response. *BMC Public Health*. 7:325, 2007.

Stefanics G, Thuróczy G, Kellényi L, Hernádi I. Effects of twenty-minute 3G mobile phone irradiation on event related potential components and early gamma synchronization in auditory oddball paradigm. *Neuroscience*. 157:453-462, 2008.

Sudan M, Kheifets L, Arah OA, Olsen J. Cell phone exposures and hearing loss in children in the Danish National Birth Cohort. *Paediatr Perinat Epidemiol*. 27:247-257, 2013.

Takahashi M1, Saito A, Jimbo Y, Nakasono S. Evaluation of the effects of power-frequency magnetic fields on the electrical activity of cardiomyocytes differentiated from human induced pluripotent stem cells. *J Toxicol Sci*. 42:223-231, 2017.

Tang J, Zhang Y, Yang L, Chen Q, Tan L, Zuo S, Feng H, Chen Z, Zhu G. Exposure to 900 MHz electromagnetic fields activates the mkp-1/ERK pathway and causes blood-brain barrier damage and cognitive impairment in rats. *Brain Res*. 1601:92-101, 2015.

Thomas S, Heinrich S, von Kries R, Radon K. Exposure to radio-frequency electromagnetic fields and behavioural problems in Bavarian children and adolescents. *Eur J Epidemiol*. 25:135-141, 2010.

Tombini M, Pellegrino G, Pasqualetti P, Assenza G, Benvenga A, Fabrizio E, Rossini PM. Mobile phone emissions modulate brain excitability in patients with focal epilepsy. *Brain Stimul*. 6:448-454, 2013.

Tong J, Chen S, Liu XM, Hao DM. [Effect of electromagnetic radiation on discharge activity of neurons in the hippocampus CA1 in rats]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi*. 29:423-427, 2013. [Article in Chinese]

Trunk A, Stefanics G, Zentai N, Kovács-Bálint Z, Thuróczy G, Hernádi I. No effects of a single 3G UMTS mobile phone exposure on spontaneous EEG activity, ERP correlates, and automatic deviance detection. *Bioelectromagnetics*. 34: 31-42, 2013.

Trunk A, Stefanics G, Zentai N, Bacskey I, Felinger A, Thuróczy G, Hernádi I. Lack of interaction between concurrent caffeine and mobile phone exposure on visual target detection: An ERP study. *Pharmacol Biochem Behav.* 124:412-420, 2014.

Trunk A, Stefanics G, Zentai N, Bacskey I, Felinger A, Thuróczy G, Hernádi I. Effects of concurrent caffeine and mobile phone exposure on local target probability processing in the human brain. *Sci Rep.* 5:14434, 2015.

Unterlechner M, Sauter C, Schmid G, Zeitlhofer J. No effect of an UMTS mobile phone-like electromagnetic field of 1.97 GHz on human attention and reaction time. *Bioelectromagnetics.* 29:145-153, 2008.

Vácha M, Puzová T, Kvícalová M. Radio frequency magnetic fields disrupt magnetoreception in American cockroach. *J Exp Biol.* 212(Pt 21):3473-3477, 2009.

Varghese R, Majumdar A, Kumar G, Shukla A. Rats exposed to 2.45GHz of non-ionizing radiation exhibit behavioral changes with increased brain expression of apoptotic caspase 3. *Pathophysiology.* 2017 Nov 14. pii: S0928-4680(17)30052-4. doi: 10.1016/j.pathophys.2017.11.001.

Vecchio F, Babiloni C, Ferreri F, Curcio G, Fini R, Del Percio C, Rossini PM. Mobile phone emission modulates interhemispheric functional coupling of EEG alpha rhythms. *Eur J Neurosci.* 25:1908-1913, 2007.

Vecchio F, Babiloni C, Ferreri F, Buffo P, Cibelli G, Curcio G, van Dijkman S, Melgari JM, Giambattistelli F, Rossini PM. Mobile phone emission modulates inter-hemispheric functional coupling of EEG alpha rhythms in elderly compared to young subjects. *Clin Neurophysiol.* 121:163-171, 2010.

Vecchio F, Buffo P, Sergio S, Iacoviello D, Rossini PM, Babiloni C. Mobile phone emission modulates event-related desynchronization of  $\alpha$  rhythms and cognitive-motor performance in healthy humans. *Clin Neurophysiol.* 123:121-128, 2012a.

Vecchio F, Tombini M, Buffo P, Assenza G, Pellegrino G, Benvenga A, Babiloni C, Rossini PM. Mobile phone emission increases inter-hemispheric functional coupling of electroencephalographic alpha rhythms in epileptic patients. *Int J Psychophysiol.* 84:164-171, 2012b.

Vecsei Z, Csathó A, Thuróczy G, Hernádi I. Effect of a single 30 min UMTS mobile phone-like exposure on the thermal pain threshold of young healthy volunteers. *Bioelectromagnetics.* 34:530-541, 2013.

Velayutham P, Govindasamy GK, Raman R, Prepageran N, Ng KH. High-frequency hearing loss among mobile phone users. *Indian J Otolaryngol Head Neck Surg.* 66 (Suppl 1):169-172, 2014.

Wallace D, Eltiti S, Ridgewell A, Garner K, Russo R, Sepulveda F, Walker S, Quinlan T, Dudley S, Maung S, Deeble R, Fox E. Cognitive and physiological responses in humans exposed to a TETRA base station signal in relation to perceived electromagnetic hypersensitivity. *Bioelectromagnetics.* 33:23-39, 2012.

Wang H, Peng R, Zhou H, Wang S, Gao Y, Wang L, Yong Z, Zuo H, Zhao L, Dong J, Xu X, Su Z. Impairment of long-term potentiation induction is essential for the disruption of spatial memory after microwave exposure. *Int J Radiat Biol.* 89:1100-1107, 2013.

Wang H, Peng R, Zhao L, Wang S, Gao Y, Wang L, Zuo H, Dong J, Xu X, Zhou H, Su Z. The relationship between NMDA receptors and microwave induced learning and memory impairment: a long-term observation on Wistar rats. *Int J Radiat Biol.* 91:262-269, 2015.

Wang H, Tan S, Xu X, Zhao L, Zhang J, Yao B, Gao Y, Zhou H, Peng R. Long term impairment of cognitive functions and alterations of NMDAR subunits after continuous microwave exposure. *Physiol Behav.* 181:1-9, 2017.

Wang K, Lu JM, Xing ZH, Zhao QR, Hu LQ, Xue L, Zhang J, Mei YA. Effect of 1.8 GHz radiofrequency electromagnetic radiation on novel object associative recognition memory in mice. *Sci Rep.* 7:44521, 2017.

Wang LF, Li X, Gao YB, Wang SM, Zhao L, Dong J, Yao BW, Xu XP, Chang GM, Zhou HM, Hu XJ, Peng RY. Activation of VEGF/Flk-1-ERK pathway induced blood-brain barrier injury after microwave exposure. *Mol Neurobiol.* 52:478-491, 2015.

Wang LF, Tian DW, Li HJ, Gao YB, Wang CZ, Zhao L, Zuo HY, Dong J, Qiao SM, Zou Y, Xiong L, Zhou HM, Yang YF, Peng RY, Hu XJ. Identification of a novel rat NR2B subunit gene promoter region variant and its association with microwave-induced neuron impairment. *Mol Neurobiol.* 53:2100-2111, 2016.

Watilliaux A, Edeline JM, L  v  que P, Jay TM, Mallat M. Effect of exposure to 1,800 MHz electromagnetic fields on heat shock proteins and glial cells in the brain of developing rats. *Neurotox Res.* 20:109-119, 2011.

Wiholm C, Lowden A, Kuster N, Hillert L, Arnetz BB, Akerstedt T, Moffat SD. Mobile phone exposure and spatial memory. *Bioelectromagnetics.* 30:59-65, 2009.

Xiong L, Sun CF, Zhang J, Gao YB, Wang LF, Zuo HY, Wang SM, Zhou HM, Xu XP, Dong J, Yao BW, Zhao L, Peng RY. Microwave exposure impairs synaptic plasticity in the rat hippocampus and PC12 cells through over-activation of the NMDA receptor signaling pathway. *Biomed Environ Sci.* 28:13-24, 2015.

Xu F, Bai Q, Zhou K, Ma L, Duan J, Zhuang F, Xie C, Li W, Zou P, Zhu C. Age-dependent acute interference with stem and progenitor cell proliferation in the hippocampus after exposure to 1800 MHz electromagnetic radiation. *Electromagn Biol Med*. 36:158-166, 2017.

Xu S, Zhou Z, Zhang L, Yu Z, Zhang W, Wang Y, Wang X, Li M, Chen Y, Chen C, He M, Zhang G, Zhong M. Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons. *Brain Res*. 1311:189-196, 2010.

Yakymenko I, Tsybulin O, Sidorik E, Henshel D, Kyrylenko O, Kyrylenko S. Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. *Electromagn Biol Med*. 35:186-202, 2016.

Yang L, Chen Q, Lv B, Wu T. Long-term evolution electromagnetic fields exposure modulates the resting state EEG on alpha and beta bands. *Clin EEG Neurosci*. 48:168-175, 2017.

Yang X, He G, Hao Y, Chen C, Li M, Wang Y, Zhang G, Yu Z. The role of the JAK2-STAT3 pathway in pro-inflammatory responses of EMF-stimulated N9 microglial cells. *J Neuroinflammation*. 7:54, 2010.

Yang XS, He GL, Hao YT, Xiao Y, Chen CH, Zhang GB, Yu ZP. Exposure to 2.45 GHz electromagnetic fields elicits an HSP-related stress response in rat hippocampus. *Brain Res Bull*. 88:371-378, 2012.

Yogesh S, Abha S, Priyanka S. Mobile usage and sleep patterns among medical students. *Indian J Physiol Pharmacol*. 58:100-103, 2014.

Yuan K, Qin W, Wang G, Zeng F, Zhao L, Yang X, Liu P, Liu J, Sun J, von Deneen KM, Gong Q, Liu Y, Tian J. Microstructure abnormalities in adolescents with internet addiction disorder. *PLoS One*. 6:e20708, 2011.

Zareen N, Khan MY, Ali Minhas L. Derangement of chick embryo retinal differentiation caused by radiofrequency electromagnetic fields. *Congenit Anom (Kyoto)*. 49:15-19, 2009.

Zhang SZ, Yao GD, Lu DQ, Chiang H, Xu ZP. [Effect of 1.8 GHz radiofrequency electromagnetic fields on gene expression of rat neurons]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 26:449-452, 2008. [Article in Chinese]

Zhang Y, Li Z, Gao Y, Zhang C. Effects of fetal microwave radiation exposure on offspring behavior in mice. *J Radiat Res*. 56:261-268, 2015.

Zhang JP, Zhang KY, Guo L, Chen QL, Gao P, Wang T, Li J, Guo GZ, Ding GR. Effects of 1.8 GHz Radiofrequency Fields on the Emotional Behavior and Spatial Memory of Adolescent Mice. *Int J Environ Res Public Health*. 14(11), 2017. pii: E1344. doi: 10.3390/ijerph14111344.

Zhao TY, Zou SP, Knapp PE. Exposure to cell phone radiation up-regulates apoptosis genes in primary cultures of neurons and astrocytes. *Neurosci Lett*. 412:34-38, 2007.

Zheng F, Gao P, He M, Li M, Wang C, Zeng Q, Zhou Z, Yu Z, Zhang L. Association between mobile phone use and inattention in 7102 Chinese adolescents: a population-based cross-sectional study. *BMC Public Health*. 14:1022, 2014.



Neurological - Report; Evidence of Neurological effects of Electromagnetic  
Radiation: Implications for degenerative disease and brain tumor  
from residential, occupational, cell site and cell phone exposures.  
Prof. Neil Cherry; 225 scientific references. 2002

**Evidence of Neurological effects of  
Electromagnetic Radiation: Implications  
for degenerative disease and brain  
tumour from residential, occupational,  
cell site and cell phone exposures.**

**Dr Neil Cherry O.N.Z.M.  
Associate Professor of Environmental Health**

**10<sup>th</sup> September 2002**

**Neil.Cherry@ecan.govt.nz**

**© Dr Neil Cherry 2002-2005**

**Human Sciences Department  
P.O. Box 84  
Lincoln University  
Canterbury, New Zealand**

# **Evidence of Neurological effects of Electromagnetic Radiation: Implications for degenerative disease and brain tumour from residential, occupational, cell site and cell phone exposures.**

**Dr Neil Cherry, O.N.Z.M.  
Associate Professor of Environmental Health  
Lincoln University, New Zealand**

**10<sup>th</sup> September 2002**

## **Abstract**

The brain it is a really sensitive bioelectromagnetic organ. Therefore it is scientifically plausible that brain will react to and be sensitive to external electromagnetic signals. It has been shown that has very strong evidence that the brain detects and responds to the Schumann Resonance signal of  $0.1\text{pW}/\text{cm}^2$ . Since the first evidence that RF radiation damages chromosomes in 1959, many independent studies have identified broken DNA stands, chromosome aberrations and altered gene expression in animal cells, human cells and in living animals and humans from EMR exposure. Microwaves, including cell phone radiation, open the Blood Brain Barrier (BBB). Exposure to RF/MW is consistently associated with headaches, fatigue, loss of concentration and memory loss. These symptoms have been called "The Radiofrequency Sickness Syndrome" or "Microwave Syndrome". Because these are subjective symptoms they have been largely dismissed in the West. These symptoms are now shown with cell phone use in a significant dose-response manner. All of these effects are linked to electromagnetic radiation's ability to alter cellular calcium ions and GABA through cellular signal transduction processes not involving heat, to reduce melatonin and damage DNA, and enhance Apoptosis. A large and growing body of epidemiological research is revealing EMR associated neurological effects, degenerative disease and brain tumour. Cell phone radiation is involved in many of the biological effects and now shows significant increases in DNA damage and brain tumours. Residential exposures down to  $0.4\text{nW}/\text{cm}^2$ , typically a thousand times stronger than the Schumann Resonance signal, and living within the vicinity of cell sites, are shown to have a causal relationship to the melatonin reduction related sleep disturbance. Therefore they will produce a host of other genotoxic and melatonin related health effects.

Key Words: Electromagnetic radiation, calcium ion efflux, GABA, genotoxicity, melatonin reduction, neurological disease, suicide, brain cancer

## **Introduction:**

Our brains are exquisitely sensitive bioelectrochemical organs that are the seat of human creativity, memory, emotions and intelligence. We use electrical signals, including charged calcium ions, to think, remember and see, to regulate the beating of our heart, and for communication in our central nervous system and between and within our cells. Human brains were proven in the 1950's and 1960's, König (1974) and Wever (1974), to be very sensitive to and reactive to extremely small, naturally occurring Schumann Resonances. The Schumann Resonances are global low frequency signals that share the same part of the spectrum as the EEG. They are generated largely by tropical thunderstorms. They

propagate around the (at the speed of light), being ducted in the resonant cavity formed between the earth and the ionosphere. König observed highly significant alteration of human reaction times associated with the intensity of the Schumann Resonances, Figure 1. He then carried out laboratory experiments and could speed people up with 10 Hz signals and slow them down with 3 Hz signals. This work was independently confirmed by Hamer (1965, 1969). Wever (1974) carried out long-term isolation experiments and showed that isolation from sunlight resulted in significantly lengthened daily rhythms. Isolation also from all EMR extended the daily period significantly more. About 30 % of subjects were desynchronized, producing very long and erratic daily rhythms. These could be corrected by the introduction of a very low intensity 10 Hz signal, similar to the primary Schumann Resonance peak.

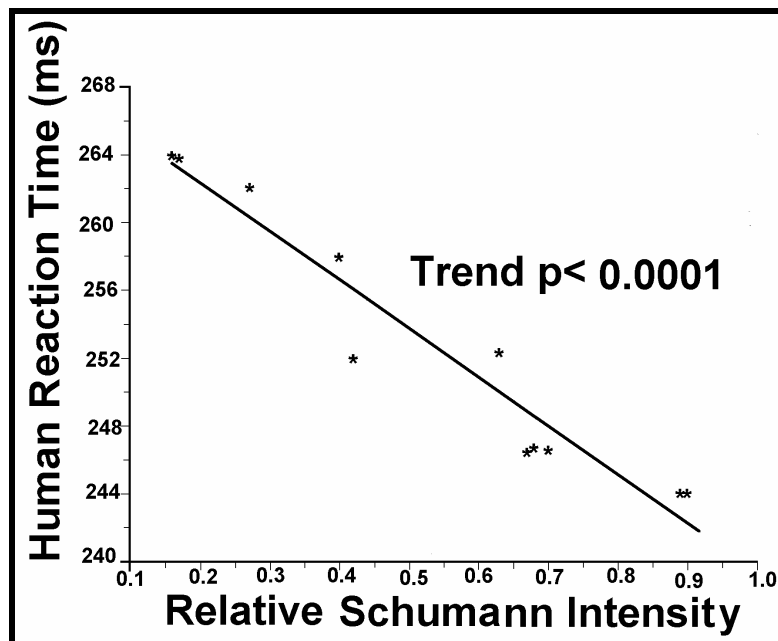


Figure 1: Human reaction times are causally correlated with natural variations in the Schumann Resonance Intensity, König (1974). The mean Schumann intensity (Relative Schumann Intensity =0.5) is 0.65mV/m or 0.1pW/cm<sup>2</sup>. The range is 0.2 to 1.2 mV/m (0.01 to 0.4pW/cm<sup>2</sup>).

The original König and Hamer experiments involved field strengths in the order of 1 V/m (0.27μW/cm<sup>2</sup>) but results were still statistically significant when 1mV/m (0.27pW/cm<sup>2</sup>) was used. The Schumann Resonances have a fundamental frequency of 7.8 Hz. The spectrum has other resonance peaks near 14.1, 20.3, 26.4 and 32.5 Hz. The three primary peaks between 7 and 21 Hz have a mean intensity of about 0.1pW/cm<sup>2</sup>, Polk (1982). Thus the early German research concluded that there was significant proof that human beings react to electromagnetic radiation at extremely low intensities, including that naturally produced and called the Schumann Resonances. They speculated that humans had evolved to use the Schumann Resonances to timing synchronization, that is, they are a Zeitgeber.

Cherry (2002) shows that the Schumann Resonance (SR) signal modulation by Solar/Geomagnetic Activity (S/GMA) modulates human melatonin, Figure 2, and causes modulation of human health effect including, cancer, cardiac, reproductive and neurological diseases and mortality, with a mean intensity of 0.1pW/cm<sup>2</sup>, with a magnetic field component about 1-3pT.

It is noted that cell sites produce signal intensities over  $0.1\mu\text{W}/\text{cm}^2$ , out to 500m to 1000 m, depending on the power and height of the tower. This is 1 million times higher than the natural SR signals that it is proven that our brains detect and use. The possibility of interference with the natural signals and the processes that they alter is strongly evident.

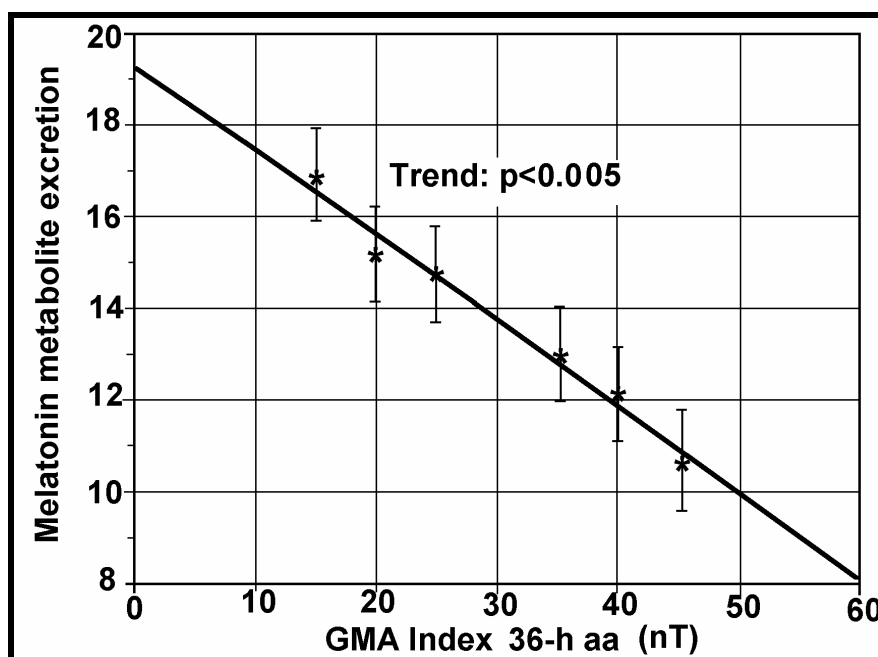


Figure 2: Reduction in the melatonin metabolite 6-OHMS in  $\mu\text{g}$  in urine from U.S. electric utility workers, as a function of the 36 hr global GMA aa-index, Burch et al. (1999b).

Figures 1 and 2 show a classically causal relationship between the Schumann Resonance signal strength, which is extremely correlated with GMA indices, with altered human reaction times and modulation of human melatonin.

A core principle of Environmental Health is understanding and appreciating the natural system before assessing the impact of human activity on people, organs and cells. The failure of authorities to appreciate this and to apply this principle, has led to massive trends in neurological illnesses from living in electric power produced ELF fields and RF/MW fields from radio and TV stations, computer screens, cordless phones, and occupational exposures of electrical workers, physiotherapists, airport staff, military, police and fire personnel, radio and TV personnel. Most recently this involves the introduction of a cellular phone network and wireless laptop systems.

Western public exposure guidelines and standards are typically in the range 0.1 to 10 billion times higher than the SR signal which is causally associated with modulation of human health effects. The evidence and conclusions of this report give a strong motivation for revising exposure standards and the development and application of safer technologies.

## Early Evidence of Neurological Symptoms from chronic radar exposure:

Evidence that radiofrequency/microwave (RF/MW) radiation also interacts with human brains at extremely low intensities comes from the U.S. Embassy in Moscow during the

1950s-1970s, Lilienfeld et al. (1978). Overall the mortality rate of Moscow personnel was 42% and in the comparative posts personnel it was 36% of the U.S. rate, showing the health employee effect and the healthier status of State Department staff through the selection of health staff.

The U.S. Embassy was deliberately irradiated by Soviet radar for over 20 years. It was aimed at the 5<sup>th</sup> floor of the west wall at one end of the Embassy Building. During most of this time the peak reading was  $5\mu\text{W}/\text{cm}^2$ , over the working hours. The internal exposures are much smaller, Pollard (1979). Mean daily exposures are typically in the range 0.01 to  $0.1\mu\text{W}/\text{cm}^2$ .

Several significant adverse health effects were identified. Several sickness symptoms were significantly increased with years of service in the Moscow Embassy, a dose-response relationship. They included Arthritis/Rheumatism (trend  $p=0.02$ ), Back Pain (trend  $p=0.04$ ), Ear problems (trend  $p=0.02$ ), Skin/Lymphatic (trend  $p=0.02$ ) and Vascular System (trend  $p=0.004$ )

The male staff who were chronically exposed to the radar signal showed a wide range of elevated neurological symptoms, some of which were significantly increased. These included depression ( $p=0.004$ ), irritability ( $p=0.009$ ), difficulty in concentration ( $p=0.001$ ), memory loss ( $p=0.008$ ). Dependents developed increased rates of cancer, including significant brain tumors, SMR = 20 (2.4-72.2). Children had increased mental and nervous conditions (RR = 5.0) and behavioural problems (RR= 2.06).

Baranski and Czerski (1976) give a description of a microwave exposure syndrome that was identified by Soviet researchers, e.g. Gordon (1966). Similar syndromes were reported in France by Deroche (1971) and in Israel by Moscovici et al. (1974). The Syndrome's symptoms included headaches, fatigue, irritability, nausea, vertigo, sleep disturbances and decreased libido. Johnson-Liakouris (1998) states that a literature review and the Lilienfeld study supports the Radiofrequency (RF) Sickness Syndrome as a medical entity. The headache symptoms were found with microwave exposure during "microwave hearing" experiments, Frey (1998) and in microwave exposure case studies, Forman et al. (1986).

The evidence was strong enough in 1982 for the Supreme Court of New York to award workers compensation for "Radiofrequency Sickness Syndrome" for chronic occupational microwave exposure to a technician servicing TV transmitters in the 87th floor of the Empire State Building, Yannon vs New York Telephone Co. The compensation also recognized that the chronic microwave exposure caused his death. Application for leave to appeal was declined. The primary expert witness in this case was Dr Milton Zaret.

### **Biological Mechanisms for Neurological Effects:**

Biological mechanism for these effects have been well identified, especially, reduced melatonin. Pulsed and modulated RF/MW radiation is also shown to induce efflux of calcium ions and GABA from brain cells.

GABA related neurotransmitters are changed in a dose response manner by 915 MHz microwaves, Figure 3. Altered GABA is shown to cause all of the neurological symptoms identified above. GABA (gamma-amino butyric acid) and glutamatergic synapses make up up to 60 % of the synapses in the CNS and 40 % in the brain, Kolomytkin et al. (1994). Hence induced alteration of GABA in the brain can have serious consequences. Figure 3

shows that a 5 minute exposure to pulsed microwaves have a dose-response effect on GABA related receptors.

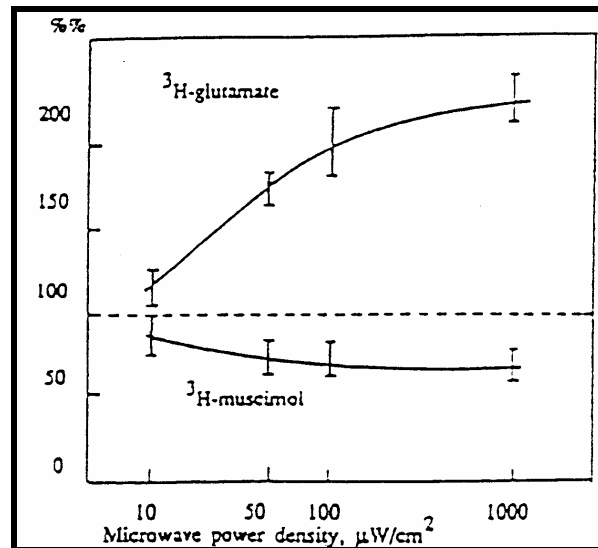


Figure 3: Exposure related alteration of GABA related molecules in rat brains exposed for 5 minutes to 915 MHz microwaves, pulsed at 16 pps. Differences from controls are still significant at  $10\mu\text{W}/\text{cm}^2$ . Kolomytkin et al. (1994)

Frey (1995) concludes that EMR affects the dopamine systems of the brain through its effects on GABA. He also notes that the dopamine-opiate systems interact with the pineal melatonin/serotonin system.

### **Altering Cellular calcium in homeostasis:**

The initial calcium ion research of Adey and Bawin was motivated by the observations that EMR altered reaction times in people, König (1974) and Hamer (1965, 1969), and monkeys, Gavalas-Medici and Day-Magdaleno (1976). Bawin, Gavalas-Medici and Adey (1973) showed alterations in cat EEGs and subsequently calcium ion efflux from cat brains under the same exposure conditions, Adey (1979). Shandala et al. (1979) show that microwaves significantly altered the EEG of animals.

Calcium ions are ubiquitous in cells throughout our bodies. The calcium ion ( $\text{Ca}^{2+}$ ) is one of the most important substances in cells.  $\text{Ca}^{2+}$  is a first, second and third signal transduction messenger, Alberts et al. (1994), Pahl (1999). Alberts et al. describes  $\text{Ca}^{2+}$  as a prominent and ubiquitous intracellular messenger. This means that factors that induce changes of cellular  $\text{Ca}^{2+}$  can cause significant changes of cells. As a signal transduction messenger  $\text{Ca}^{2+}$  initiates and regulates many cellular processes, such as melatonin production. Given that EMR induces changes in cellular calcium ions it is reasonable to investigate whether EMR induces changes in melatonin. This biological plausibility of ELF detection by the brain is significantly strengthened by the observation that mammal brains contain and use phase-locked loop circuitry to detect and react to incoming ELF signals, Ahissar et al. (1997). Hence our brains contain a highly efficient, tuned FM receiver, Motluk (1997).

Chemical substances, such as TPA, are cancer promoters. They operate by altering the calcium ions. They cause calcium ion influx, which stops a damaged cell from going into apoptosis (programmed cell death) so that the cancer cell survives. Certain electromagnetic radiation combinations cause calcium ion influx, i.e. promoting cancer,

while other causes of calcium ion efflux, promoting apoptosis. Balcer-Kubiczek (1995) describes the ways in which TPA at low concentrations are able to switch the effect of calcium ion elevation from cell death to cell proliferation, probably by the activation of protein kinase C.

Dr Carl Blackman reviewed the extensive research literature on calcium ion efflux. He was well qualified to do this since he and his group at the U.S. E.P.A. had been responsible to replicating and extending all of the research shown in other laboratories. Blackman (1990) concludes:

**"Taken together, the evidence overwhelmingly indicates that electric and magnetic fields can alter normal calcium ion homeostasis and lead to changes in the response of biological systems to their environment".**

Blackman (1990) concludes that calcium ion efflux/influx is an established biological effect of EMR exposure and it changes the biological response of cells. Because modulation frequencies are critically involved, and low intensity exposures are observed under some circumstances to produce greater effects than some higher exposure conditions, resonant interactive processes are indicated and heating is definitely not involved except to establish a homeostatic range.

Blackman's group confirmed and significantly extended the "windows" concept of  $\text{Ca}^{2+}$  efflux, as well as aspects of homeostasis, involving tissue temperature for example.  $\text{Ca}^{2+}$  efflux is a function of modulation frequencies. Frequencies out to 510 Hz produce significant  $\text{Ca}^{2+}$  efflux at some frequencies, but not at other frequencies on either side, Blackman et al. (1988). Power-Density windows are also identified, Bawin and Adey (1976), Blackman et al. (1989). The lowest intensity that has been published showing significant  $\text{Ca}^{2+}$  efflux is 0.00015 W/kg, Schwartz et al. (1990). This involved a 16 Hz modulation carried on a 240 MHz carrier. This is equivalent to  $0.08\mu\text{W}/\text{cm}^2$ .

Blackman et al. (1990a) showed the importance of the local static magnetic field. Blackman et al. (1991) showed that  $\text{Ca}^{2+}$  efflux occurred for tissue temperatures of  $36^\circ\text{C}$  and  $37^\circ\text{C}$  and not at  $35^\circ\text{C}$  and  $38^\circ\text{C}$ .  $\text{Ca}^{2+}$  efflux is demonstrably not a thermal effect. It occurs at extremely low non-thermal levels and is a function of frequency, modulation frequency and it occurs in exposure windows. This appears to be a form of resonant interaction.

In some quarters the RF-Thermal View still dominates. This has been challenged many times since the Second World War. For example, Dr Adey gave the introductory paper to a 1974 conference, Adey (1975), on the effects of EMR on the nervous system. In this paper he states:

**"Even a recent review body of the World Health Organization decided after discussion to dismiss from its concerns possible biological effects that might occur in the absence of significant heating. It has become clear, however, that interactions with the mammalian central nervous system can be reliably produced by oscillating electric and electromagnetic fields without significant heating of tissues."**

Blackman et al. (1991) comment that the windowing aspects of  $\text{Ca}^{2+}$  efflux could be very good reasons why experimental outcomes have been difficult to confirm in some laboratories. Everything may appear to be the same but the local magnetic field is



different and completely changes the results. High exposure levels that raise the temperature outside the homeostatic range will produce no effects. Hence only non-thermal exposures produce these effects. Thus people are moving through constantly changing fields at home, at work and in the environment. They pass through windows of effect and no effect all the time. The cumulative effect of the 'effect' windows produces dose-response increases in health effects associated with extremely low mean exposures. The calcium ion effects are shown in brain tissue and heart muscle tissue, implicating neurological and cardiac effects.  $\text{Ca}^{2+}$  efflux from pinealocytes (cell in the pineal gland) is likely to reduce melatonin production. This has implications for many kinds of sickness, cancer, miscarriage, neurological disease etc... because melatonin is a very potent free radical scavenger and

### **EMR Reduces Melatonin in Animals and People**

DNA strand breaks, Chromosome Aberrations, impaired immune system competence and many other biological and health effects, are caused by reduced melatonin, Reiter and Robinson (1995). Light-at-night and electromagnetic radiation, are proven to reduce melatonin and hence pose significant adverse health effects.

Light-at-night and electromagnetic radiation, are proven to reduce melatonin and hence pose significant adverse health effects. The evidence for EMR is summarized here. Rosen, Barber and Lyle (1998) state that seven different laboratories have reported suppression of nighttime rise in pineal melatonin production in laboratory animals. They show that a 50  $\mu\text{T}$ , 60 Hz field with a 0.06 $\mu\text{T}$  DC field, over 10 experiments, averages a 46% reduction in melatonin production from pinealocytes. Yaga et al. (1993) showed that rat pineal response to ELF pulsed magnetic fields varied significantly during the light-dark-cycle. They found that the rate-limiting enzyme in melatonin synthesis, N-acetyltransferase (NAT) activity showed that magnetic field exposure significantly suppressed NAT during the mid- to late dark phase.

Seventeen studies from show that ELF and RF/MW exposure reduces melatonin and enhances serotonin in people. Evidence that EMR reduced melatonin in human beings commenced with Wang (1989) who found that workers who were more highly exposed to RF/MW had a dose-response increase in serotonin, and hence indicates a dose-response reduction in melatonin. Sixteen studies have observed significant EMR associated melatonin reduction in humans. They involve a wide range of exposure situations. This includes 16.7 Hz fields, Pfluger et al. (1996); 50/60 Hz fields, Wilson et al. (1990), Graham et al. (1994), Wood et al. (1998), Karasek et al. (1998), Burch et al. (1997, 1998, 1999a, 2000), Juutilainen et al. (2000) and Graham et al. (2000); combination of 60 Hz fields and cell phone use, Burch et al. (1997, 1999a); VDTs ELF/RF exposures, Arnetz et al. (1996), and a combination of occupational 60Hz exposure and increased geomagnetic activity around 30nT, Burch et al. (1999b). Two recent studies recorded significant melatonin reduction in women in EMF residential exposure situations, Davis et al. (2002) and Levallois et al. (2002).

The eighteenth human melatonin reduction study is from 6.1-21.8 MHz SW RF exposure as reported during the shutting down process of the Schwarzenburg shortwave radio tower, Professor Theo Abelin (seminar and pers.comm.). Urinary melatonin levels were monitored prior to and following the closing down of the Schwarzenburg short wave radio transmitter. This showed a significant rise in melatonin after the signal was turned off.

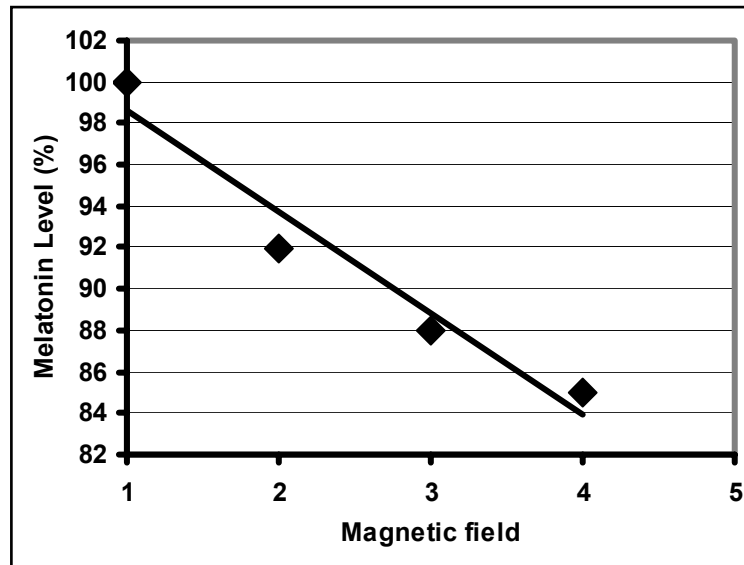


Figure 4: Human melatonin reduction from residential field exposures, the horizontal graph scale is in multiples from the lowest exposure (1), Davis (1997).

### Schwarzenburg Study:

The Swiss research, Altpeter et al. (1995, 1997) - The Schwarzenburg Study) found a causal relationship between sleep disturbance and subsequent chronic fatigue, and short-wave radio exposures at extremely low mean levels. A wide range of symptoms were significantly elevated in a dose response manner, especially for those aged more than 45 years. In a multivariate analysis only the RF exposure was independently significantly associated with sleep disturbance,  $p < 0.01$ .

The causal relationship between RF radiation exposure and deterioration in sleep quality is identified through a significant dose response relationship ( $p < 0.001$ ), Figures 5 and 6, improvements in sleep quality which changing the direction of the beams and turning the transmitter off, and reduced melatonin as the biological mechanism.

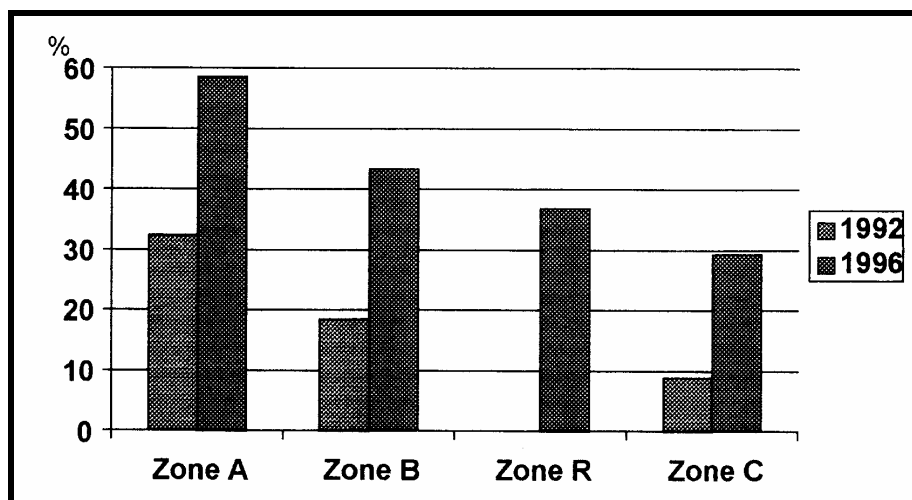


Figure 5: Adult Sleep Disturbance with RF exposure at Schwarzenburg, Switzerland, Altpeter et al. (1997).

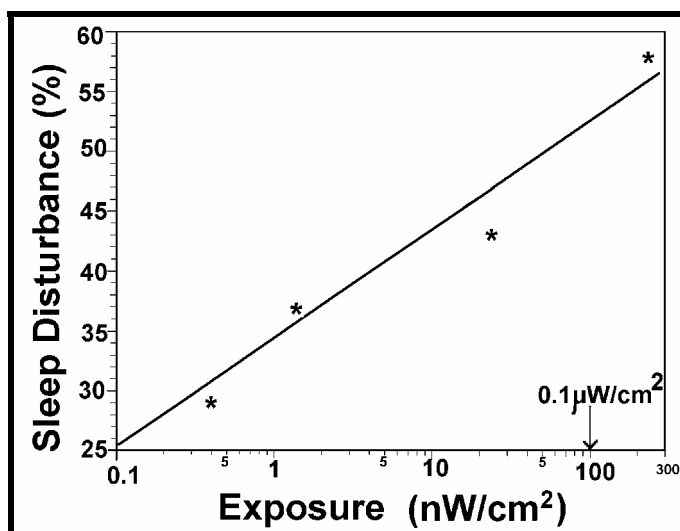


Figure 6: Dose-response relationship for Sleep Disturbance at Schwarzenburg with exposure in  $\text{nW}/\text{cm}^2$ . Note:  $1\text{nW}/\text{cm}^2 = 0.001\mu\text{W}/\text{cm}^2$

Groups B, R and C are all exposed to a mean RF signal of less than  $0.1\mu\text{W}/\text{cm}^2$  and they experienced highly significant sleep disturbance and reduced melatonin. Since sleep disturbance and melatonin reduction has been observed with cell phone exposure, Mann and Roschke (1995) and Burch et al. (1997), these observations also apply to cell sites. Assuming a normal sleep disturbance of 10 %, the approximate exposure level threshold for zero additional effect is near  $1\text{pW}/\text{cm}^2$ , near the natural level for the Schumann Resonances.

As an experiment, the transmitter was secretly turned off for three days. Sleep quality improved in all three groups being studied. Figure 7 shows Groups A and C.

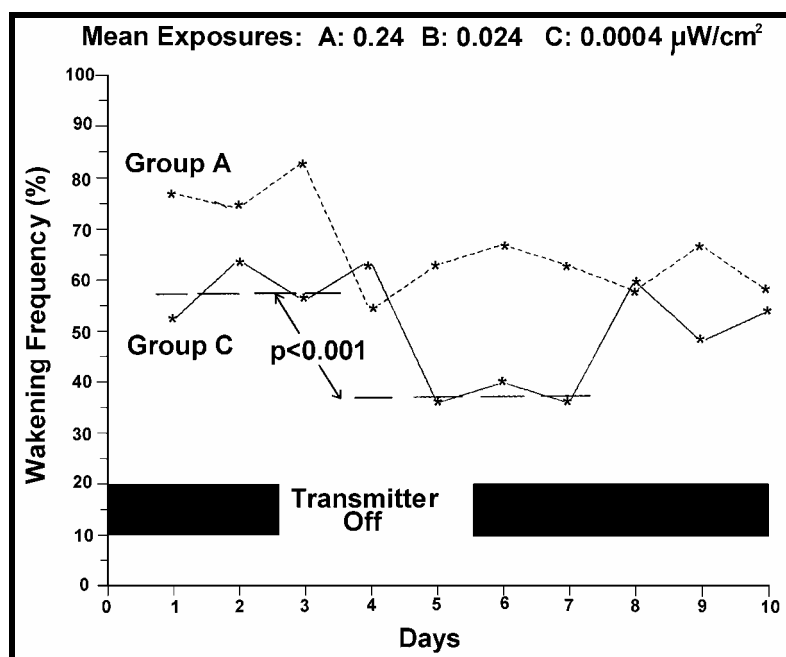


Figure 7: Sleep disturbance in people exposed to a short-wave radio stations which was turned off for three days, Altpeter et al. (1995), showing the highest exposed Group A, and lowest exposed Group C.

Both Groups show a delayed improvement in sleep of one to two days. The reduced wakening averaged over days 4 to 6 compared with days 1 to 3, for group A, and days 5

to 7 compared with days 1 to 4 for group C, are highly significantly reduced,  $p < 0.001$ . Thus a significant ( $p < 0.001$ ) improvement in sleep quality is associated with a measured 24 hour mean and median exposure of 0.1 mA/m (0.4 nW/cm<sup>2</sup>).

Human melatonin was sampled from urine in the morning. This is relatively ineffective because the important measure is the nocturnal peak. Altpeter et al. note that "Persons reporting sleep disorders, however, tend to have lower melatonin levels." When the decision was made to close down the transmitter permanently, melatonin readings were taken from a large group of residents before and after the closure. This showed a significant increase in melatonin following the closure, Professor Theo Abelin pers. Comm - seminar).

Two herds of 5 cows each, had salivary melatonin sampled several times a day, including night-time. The "exposed" herd as at 500 m from the tower with a mean exposure of 0.095  $\mu\text{W}/\text{cm}^2$ . Their mean melatonin levels were 17.7 pg/ml compared with 19.0 pg/ml for the "unexposed" cows whose measured mean exposure as 0.00022  $\mu\text{W}/\text{cm}^2$ . Figure 8 shows the melatonin for these two herds during the experiment involving turning the tower off.

The small number of cows makes it difficult to show a significant difference. There is a persistent phase shift in the nocturnal melatonin peak with the exposed cows showing a delay. This reduced when the transmitter was off but returned when it was turned on. The exposed cows have lower mean melatonin prior to the off period. It rises progressively while the transmitter is off and is significantly higher on the third night. It then drops significantly when the transmitter is turned on again. This shows the "classic" effect of EMR reduction of melatonin. The "low" exposure cow's melatonin drops when the transmitter is turned on.

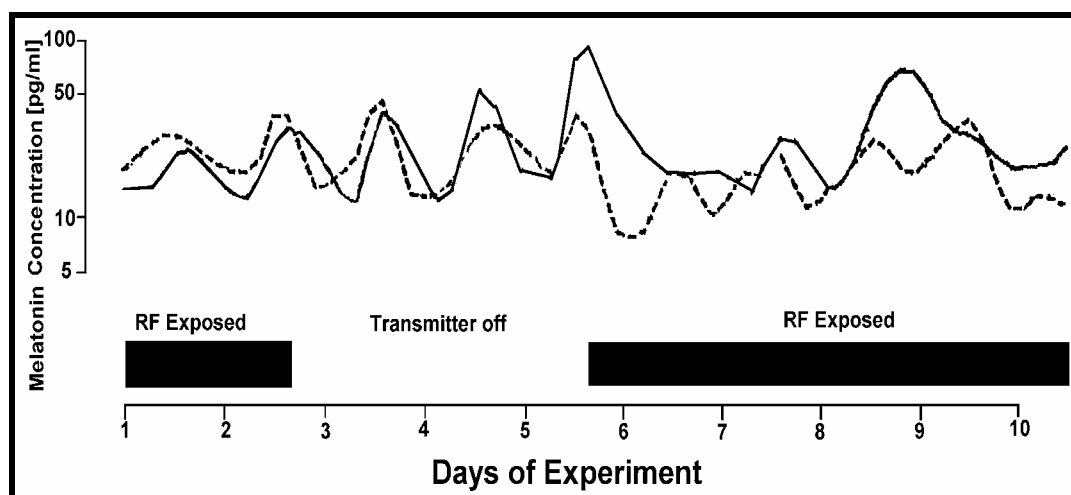


Figure 8: Salivary melatonin from two herds of 5 cows, one exposed at 500 m, 0.095  $\mu\text{W}/\text{cm}^2$ , (solid line) and one "unexposed" at 4000 m, 0.00022  $\mu\text{W}/\text{cm}^2$ , (dashed line).

The causal relationship with human sleep disturbance is strong evidence of a significant neurological effect of RF radiation on people, associated with mean exposures down to less than 0.4 nW/cm<sup>2</sup>. Hence, it is highly likely that cell phone users, with brain exposures many millions of times higher than the Schwarzenburg exposure levels, will experience significant neurological effects. The significant bovine behavioural effects of extremely low RF exposure is confirmed by Löscher and Käs (1998).

Table 1: Odd's ratios for an increase in 24-hour average exposure from 1 to 10 mA/m (0.04 to 3.8 $\mu$ W/cm<sup>2</sup>) adjusted for age, sex, attribution and duration of time lived at the same place

Symptoms	OR	95% Confidence Intervals
Nervosity (Anxiety)	2.77	1.62 - 4.74
Diff. in falling asleep	3.35	1.86 - 6.03
Diff. in maintaining sleep	3.19	1.84 - 5.52
Joint pain	2.46	1.37 - 4.43
Limb pain	2.51	1.15 - 5.50
Cough and sputum	2.80	1.18 - 6.64

All of the symptoms in Table 1 are consistent with reduced melatonin, Reiter and Robinson (1995). When the symptoms are ranked by exposure zone they form a dose-response relationship, Table 2. All of the symptoms in Table 1, except for cough and sputum, show very highly significant dose-response trends. Significant trends are also seen for Psychovegetative Index, Feeling Body excitement and Constipation. Non-significant trends are seen for Disturbed Concentration, Stomach pain and Neck and Shoulder pain. It is a common experience that lack of sleep, anxiety and depression lead to many other illnesses and symptoms.

Table 2: Complaints by Zones for all ages, showing the p-value for the trend.

Symptoms	Zone A(%)	Zone B (%)	Zone C (%)	Trend p-value
Nervousness (Anxiety)	25.0	18.0	7.0	<0.001
Difficulty in falling asleep	22.9	17.6	6.7	<0.001
Difficulty in maintaining sleep	32.4	18.5	8.9	<0.001
General weakness and tiredness	22.0	13.0	6.0	<0.001
Limb pain	14.3	6.7	3.3	0.003
Joint pain	22.9	10.1	10.0	0.004
Psychovegetative Index	12.5	5.2	3.4	0.010
Feeling body excitement	7.6	5.9	1.1	0.018
Constipation	7.6	6.7	1.7	0.034
Disturbed concentration	7.6	2.5	2.8	0.083
Stomach pains	9.5	5.9	3.9	0.152
Neck and shoulder pain	17.1	15.1	10.0	0.182

### Other Neurological Effects:

Since it is now established that EMR alters calcium ions, GABA and melatonin, including overwhelming evidence for melatonin reduction in people, it is expected that EMR exposure will produce observable neurological effects, especially those that are known to be related to calcium ions, GABA or melatonin reduction.

### Recent Research results from cell phone radiation exposure:

In recent years research into the biological effects of cell phones have revealed many significant effects, especially neurological effects, Table 3.

**Table 3: Biological effects shown by mainly government and industry funded research that associates cell phone radiation with the following symptoms:**

- Alters brain activity including EEG, Von Klitzing (1995), Mann and Roschkle (1996)
- Disturbs sleep. Mann and Roschkle (1996), Bordely et al. (1999)
- Alters human reaction times, Preece et al. (1999), Induced potentials, Eulitz et al. (1998), slow brain potentials, Freude et al. (1998), Response and speed of switching attention (need for car driving) significantly worse, Hladky et al. (1999). Altered reaction times and working memory function (positive), Koivisto et al. (2000).
- Causes memory loss, concentration difficulties, fatigue, and headache, in a dose response manner, (Mild et al. (1998)). Headache, discomfort, nausea, Hocking (1998).

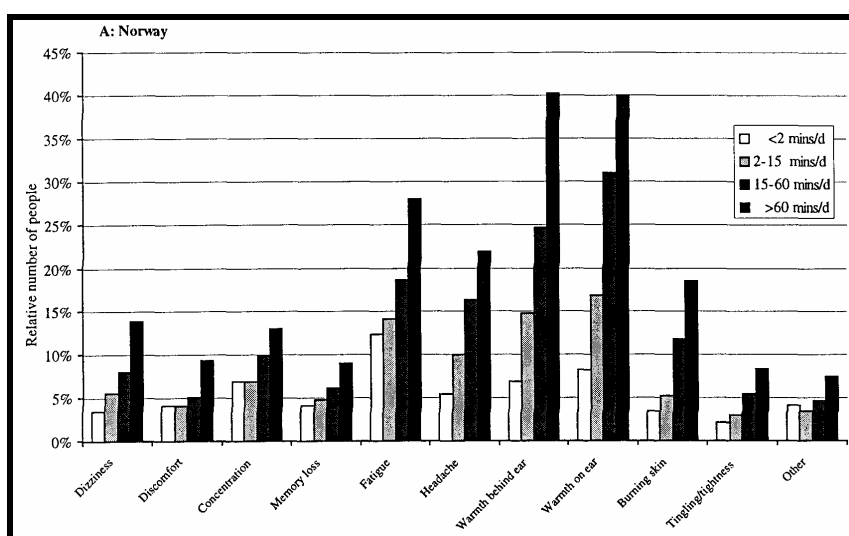


Figure 9: Prevalence of symptoms for Norwegian mobile phone users, mainly analogue, with various categories of length of calling time per day, Mild et al. (1998).

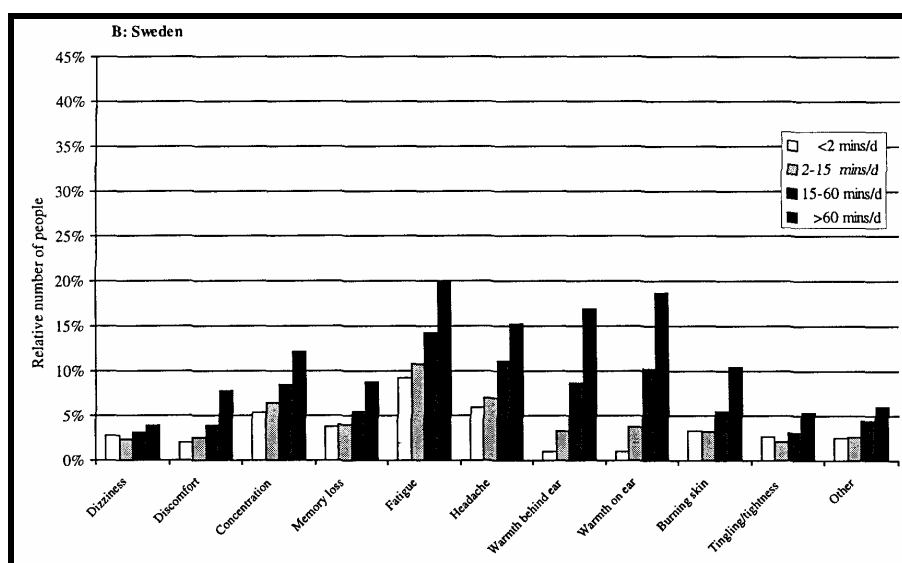


Figure 10: Prevalence of symptoms for Swedish mobile phone users, mainly digital, with various categories of length of calling time per day, Mild et al. (1998).

These are the same symptoms that have frequently been reported as "Microwave Sickness Syndrome" or "Radiofrequency Sickness Syndrome", Baranski and Czerski (1976) and Johnson-Liakouris (1998).

- A Fifteen minute exposure, increased auditory brainstem response and hearing deficiency in 2 kHz to 10 kHz range, Kellenyi et al. (1999).
- Highly significant Increased permeability of the blood brain barrier for 915 MHz radiation at SAR =0.016-0.1 ( $p=0.015$ ) and SAR = 0.1-0.4 ( $p=0.002$ ); Salford et al. (1994).
- Significant changes in local temperature, and in physiologic parameters of the CNS and cardiovascular system, Khdnisskii, Moshkarev and Fomenko (1999).
- Reduces the pituitary production of Thyrotropin (Thyroid Stimulating Hormone, TSH):

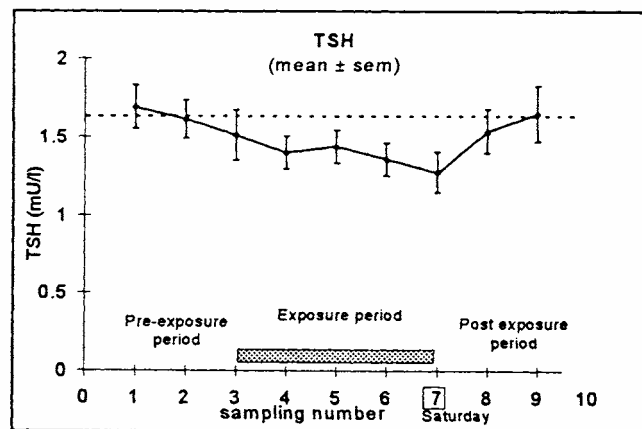


Figure 11: A significant reduction in Thyrotropin (Thyroid Stimulating Hormone) during cell phone use, de Seze et al. (1998).

- Decreases in sperm counts and smaller tube development in testes, Dasdag et al. (1999).
- Increases embryonic mortality of chickens, Youbicier-Simo, Lebecq and Bastide (1998).
- Increases blood pressure, Braune et al. (1998).
- Reduces melatonin, Burch et al. (1997).
- Breaks DNA strands (Verschaeve et al. (1994), Maes et al. (1997), Phillips et al. (1998)).
- Produces an up to three-fold increase in chromosome aberrations in a dose response manner from all cell phones tested, Tice, Hook and McRee, reported in Microwave News, April/May 1999.
- Doubles c-fos gene activity (a proto oncogene) for analogue phones and increases it by 41 % for digital phones, Goswami et al. (1999), altered c-jun gene, Ivaschuk et al. (1997), Increased hsp70 messenger RNA, Fritiz et al. (1997).

- Increase Tumour Necrosis Factor (TNF), Fesenko et al. (1999)
- DNA synthesis and cell proliferation increased after 4 days of 20 min for 3 times/day exposure. Calcium ions were significantly altered, French, Donnellan and Mc Kenzie (1997). Decreased cell proliferation, Kwee and Raskmark (1997), Velizarov, Raskmark and Kwee (1999)
- Doubles the cancer in mice, Repacholi et al. (1997).
- Increases human brain tumor rate by 2.5 times (Hardell et al. (1999)). Associated with an angiosarcoma (case study), Hardell (1999), significant increases in Brain Cancer, Hardell et al. (2000, 2002) and for Astrocytoma Hardell et al. (2002a).

An objective and independent scientific assessment would clearly state, cell phones are a strong risk factor for all of the adverse health effects identified for EMR. Hence, although a specific study is yet to be carried out, there is extremely strong evidence to conclude that cell phones are a risk factor for breast cancer. The biological mechanisms involving hormone change and altered cellular function and damage, and neurological effects, strongly supports the hypothesis that neurological effects found in association with EMR exposures are highly likely to be seen from chronic use of cell phones.

#### **Alzheimer's disease:**

Sobel et al. (1995) analysed three independent studies about AD and EMR exposure. All three studies had a consistent OR (2.9, 3.1, and 3.0). The combined results were very highly significant, OR = 3.0, 95%CI: 1.6-5.4,  $p < 0.001$ , and for women OR = 3.8, 95%CI: 1.7-8.6,  $p < 0.001$ . They concluded that the most obvious possibly etiological relevant exposure is that of electromagnetic fields.

Sobel et al. (1996) found that workers in industries with likely electromagnetic field exposure have a very significant ( $p = 0.006$ ) increase in incidence of Alzheimer's disease, OR = 3.93, 95% CI: 1.5-10.6. For males the adjusted odds ratio was 4.9, 95% CI: 1.3-7.9,  $p = 0.01$ , and for females, OR = 3.40, 95% CI: 0.8-16.0,  $p = 0.01$ . They note that:

**“These results are consistent with previous findings regarding the hypothesis that electromagnetic field exposure is etiologically associated with the occurrence of AD.”**

Sobel and Davanipour (1996) outline the etiological process they hypothesize by which EMR produces Alzheimer's disease.

- The first step involves EMR exposure upsetting the cellular calcium ion homeostasis through calcium ion efflux from cells increasing the intracellular calcium ion concentrations. This cleaves the amyloid precursor protein to produce soluble amyloid beta (sA $\beta$ ).
- sA $\beta$  is quickly secreted from cells after production, increasing the levels of sA $\beta$  in the blood stream. sA $\beta$  then binds to Apolipoprotein E and apolipoprotein J to be transported to and across the Blood Brain Barrier.



- Over time, when sufficient sA $\beta$  have been transported to the brain, a cascade of further events lead to the formation of insoluble neurotoxic beta pleated sheets of amyloid fibril, senile plaques, and eventually AD.

The biological mechanism for EMR to cause Alzheimer's disease is well advanced and entirely plausible, commencing with calcium ion efflux.

### **Multiple Sclerosis in Danish Electric Utility Workers:**

A study of 26,124 men working in Danish utility companies were studied for their incidence of multiple sclerosis (MS) in relation to average work-related exposure to electromagnetic fields. A small group of 15 men were shown to have a dose-response incidence of MS as a function of EMF exposure, Figure 12.

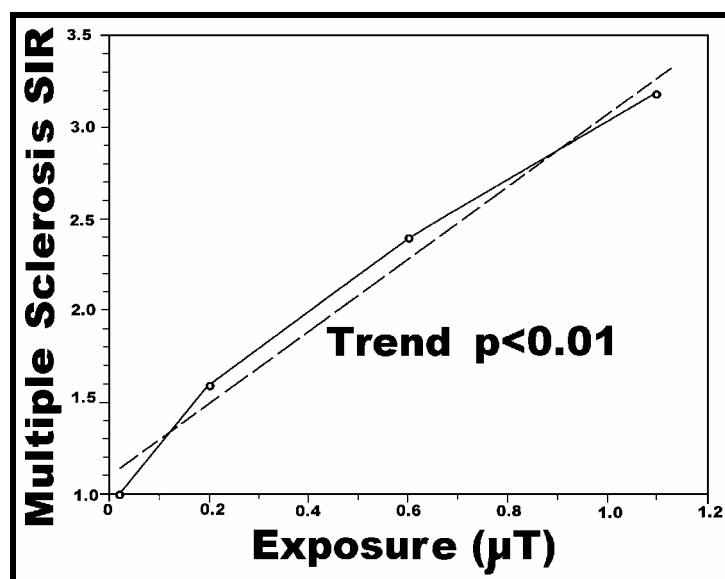


Figure 12: Dose response relationship of Multiple Sclerosis for a small group (N=15) of men occupationally exposed to typical peak magnetic fields in a Danish utility company, Johansen et al. (1999).

The authors conclude that they find no support for the hypothesis. In fact, despite the small sample size, their data shows very strong support for the hypothesis that EMR is associated with adverse neurological effects at extremely low mean exposure levels.

### **Suicide in U.S. Electric Utility Workers:**

A very large study of men working in U.S. electric utility companies included monitoring time weighted average ELF exposures of 2842 people and the identification of 536 deaths from suicide and 5348 controls. For recent exposure and 1 to 5 years of recent exposure there were significant dose-response relationships with cumulative exposure to electromagnetic fields. The recent exposure result is shown in Figure 13.

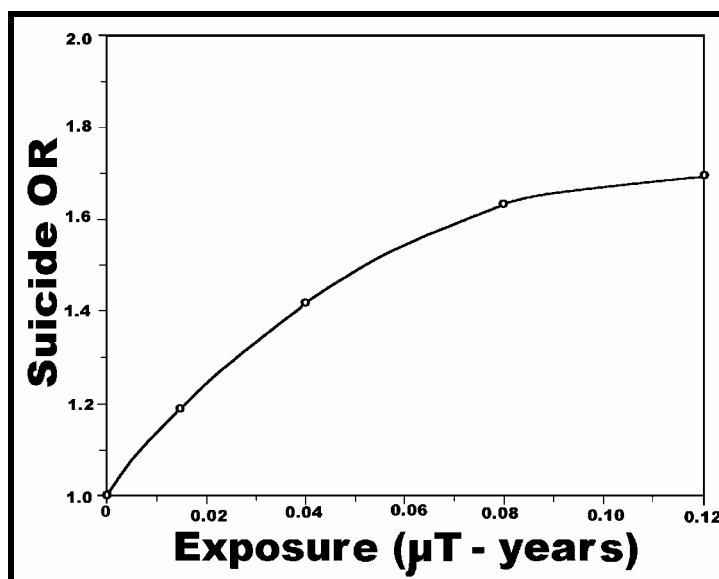


Figure 13: Dose response relationship of Suicide after recent monitored exposure to cumulative 50 Hz magnetic fields for men <50 years, adjusted for work, class, location and exposure to sunlight and solvents, Wijngaarden et al. (2000).

This confirms the results of Perry et al. (1981) who found a highly significant association between suicide and the exposure to magnetic fields from High Voltage Powerlines. Baris and Armstrong (1990) also found RF exposure shows a significant 53% increase in suicide or British Radio and Radar Mechanics, and 156 % increase for Telegraph radio operators. EMR is significantly associated with Clinical Depression, Verkasalo et al. (1997); Psychological symptoms, Beale et al. (1997); and ALS, Savitz et al. (1998a,b). Beale et al. found significant dose-response relationships for several symptoms including depression and anxiety

Non-linear response for neurological effects at extremely low exposure levels are evident in the three studies presented here for sleep disturbance, multiple sclerosis and suicide

### **MND/ALS, Parkinson's and Alzheimer's Disease:**

Welders are occupationally exposed to a combination of lead and strong ELF/RF/MW fields. Welders have increased incidence of MND, OR = 5.3 and for electric plating OR = 8.0, 95%CI: 0.9-72, Strickland et al. (1996).

Electric utility workers are frequently exposed to elevated electric and magnetic fields and sometimes to electric shocks that send high currents through their bodies, including the Motor Neuron part of their central nervous system (CNS). Overall reported electromagnetic field exposures gave for MND/ALS, OR = 3.8, 95%CI: 1.4-13.0. For electric shocks producing unconsciousness, OR = 2.8, 95%CI: 1.2-9.9.

Parkinson's disease was also significantly elevated from ELF exposure, OR = 2.7, 95%CI: 1.1-7.6, Deapen and Henderson (1986). An independent study by Davanipour et al. (1997) compared MND/ALS rates between non-electrical and electrical occupations. They found that the higher the exposure the higher the rate of MND, Figure 14. Savitz, Loomis and Tse (1998) researched neurodegenerative disease and electrical occupations and found elevated Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic

Lateral Sclerosis (ALS/MND). The highest rates were found in a very highly exposed group, the power plant operators:

**For AD, Adj OR = 2.6, 95%CI: 1.3-5.1.**

**For PD Adj OR = 2.1, 95%CI: 0.9-4.7.**

**For MND Adj OR = 4.8, 95%CI: 1.9-12.4.**

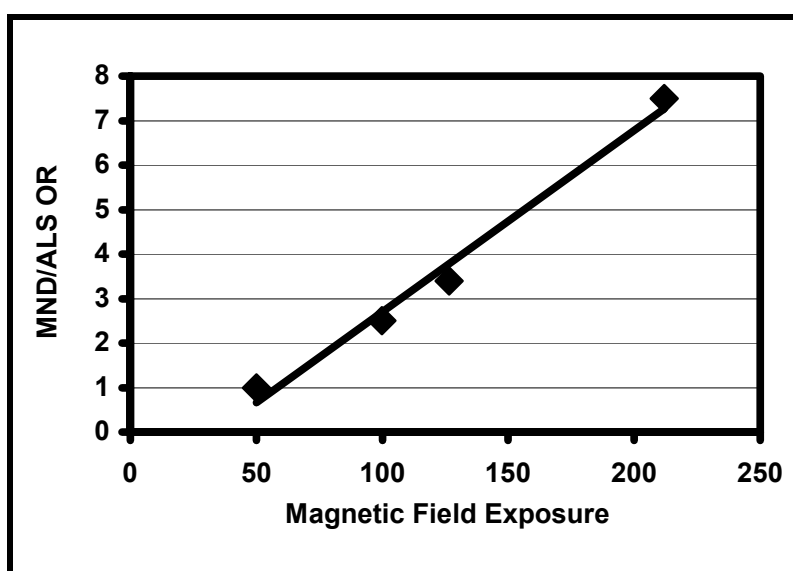


Figure 14: Dose-response increase in MND/ALS from chronic magnetic field exposures in electric utility workers,  $p < 0.02$ , Davanipour et al. (1997)

A follow-up study, Savitz, Checkoway and Loomis (1998) also found a positive association with duration of electric occupational work and MND (ALS),  $RR = 2.0$ , 95%CI: 0.7-6.0. They also found that the longer you worked in these electromagnetic fields the higher the MND rate rose, Figure 15.

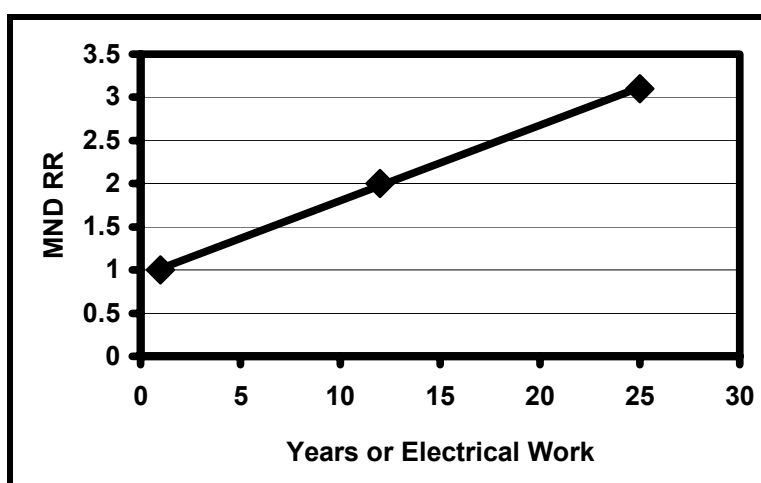


Figure 15: A significant dose-response relationship ( $p < 0.001$ ) between years of electrical work and MND (ALS), Savitz, Checkoway and Loomis (1998).

Electric utility workers in Denmark have the same risk factor for MND as U.S. utility workers, Figure 16. These three dose-response studies of EMF exposure show a causal link between chronic exposure to EMF and Motor Neuron Disease.

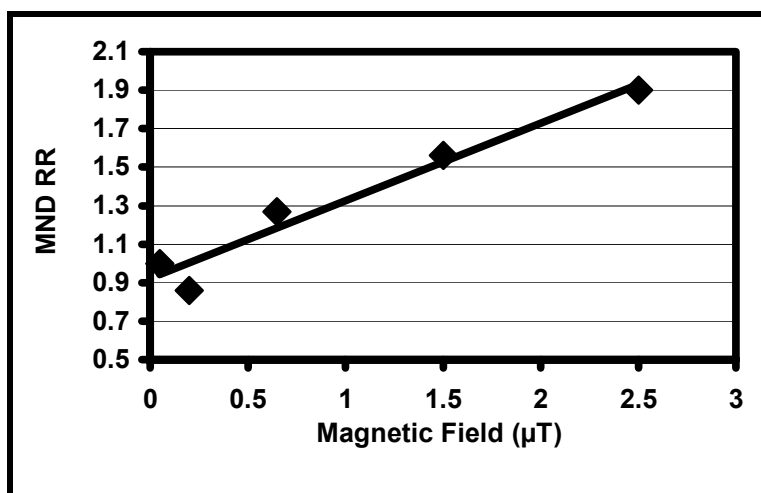


Figure 16: A significant dose-response ( $p < 0.0001$ ) increase in MND correlated with long-term mean ELF magnetic field exposures in electric utility occupations, Johansen (2000).

A recent review of Neurodegenerative Diseases in relation to EMF, Ahlbom (2001), identified 7 studies involving MND/ALS and electrical workers. When they were appropriately grouped, each group shows a significantly elevated MND rate, Table 4.

Table 4: Pooling across groups of studies on EMF and ALS, Ahlbom (2001).

Pooled studies	Number of studies	RR	95%C.I.
All	7	1.5	1.2-1.7
Clinically and ALS society based studies	3	3.3	1.7-6.7
Mortality registry and census based studies	2	1.3	1.1-1.6
Utility cohorts studies	2	2.7	1.4-5.0

This review confirms that EMF exposure in various situations significantly increases the incidence and mortality of MND/ALS.

### Epidemiology of Brain Tumour:

Eminent academic epidemiologist Dr John Goldsmith reviewed the research of RF/MW health effects. He concludes, Goldsmith (1995):

**“There are strong political and economic reasons for wanting there to be no health effect of RF/MW exposure, just as there are strong public health reasons for more accurately portraying the risks. Those of us who intend to speak for public health must be ready for opposition that is nominally but not truly, scientific. At present there seems to be little interest in or understanding of epidemiologic information among regulatory bodies that should provide protection.”**

Goldsmith (1997):

**“Available data suggest that RF radiation be considered a carcinogenic risk, a position already taken in an internal U.S. E.P.A. document in 1990 when there was much less evidence of the potential harmfulness of RF radiation.”**

The evidence in this report confirms Dr Goldsmith's conclusions.

## **Early evidence of brain tumor associated with EMR exposure**

Our strong attraction to the evident benefits of electronic technology easily masks the very strong evidence of the adverse health effects in our brains and bodies which radiation from this technology causes. This situation was described very clearly by Zaret (1977):

**“As we are all well aware, many special societal benefits have been derived from the electronic revolution. What has not yet been established are the risks associated with exposure to stray radiation. In this context, my purpose in writing is to call attention to one largely over-looked possibility, that nonionizing radiation as an atmospheric pollutant may be carcinogenic.”**

**“Despite the paucity of published information a number of clusters, each by definition consisting of 2 or more cases, are known to exist.”**

**“Regarding the clusters of our immediate concern, one instance of brain tumors (2 cases with astrocytoma) appeared in a small group of workers (about 18) servicing microwave communication equipment.”**

**“Space limitations do not permit my developing a rationale nor citing the large number of supportive references already at hand, beginning with Heller and Teixeira-Pinto in 1959, which demonstrate that nonionizing radiation can induce mutagenesis.”**

Zaret (1977) identifies 2 cases of astrocytoma (the most common primary brain tumour) in a group of 18 microwave exposed workers. Age standardized astrocytoma rates in the 1970's were about 6 per 100,000 p-yrs. Assuming a period of 25 years for these workers' exposures, this gives  $RR = 74.1$ , 95%CI: 15.0-367,  $p < 0.0001$ , which is extremely significant. Heller and Teixeira-Pinto (1959) showed that pulsed RF radiation significantly increased chromosome damage.

### **Brain Tumour with VDT exposure:**

Beall et al. (1997) found significant increases in brain tumour, especially glioma, among long-term workers using computers who are exposed to a mix of ELF and RF radiation from the VDTs. For long-term computer users, Engineering/technical users show a non-significant dose response, but computer programmers show a significant dose-response relationship, Figure 17.

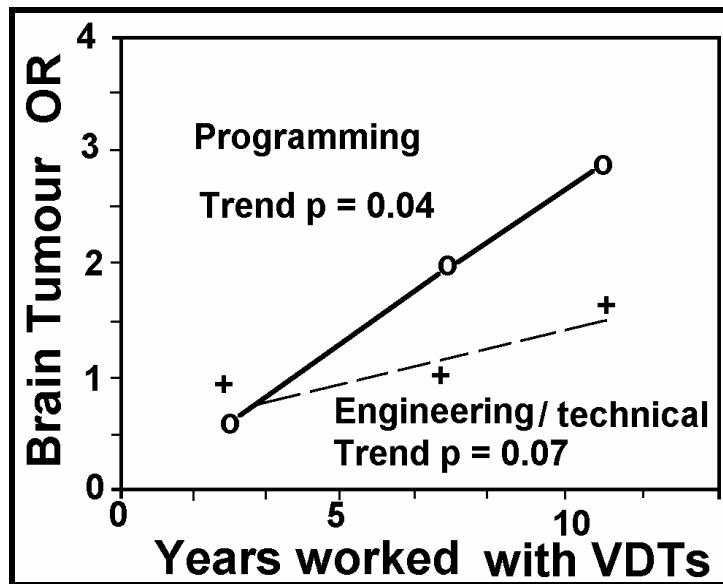


Figure 17 Dose-response increases in brain tumour from years of working with computers, Beall et al. (1997).

A search of the epidemiological literature, with the assistance of MEDLINE, and medical school libraries, reveals 96 studies covering over 420 separately exposed groups, that reveal that brain tumour incidence or mortality is increased with EMR exposure across the spectrum. Table 6 lists 28 studies showing dose response or significant dose response increases in brain tumour incidence with EMR exposure.

**Table 5: Summary table of studies and groups showing elevated brain cancer from exposure to electromagnetic radiation across the EMR spectrum.**

<b>Total studies showing elevated brain cancer:</b>	<b>96</b>
<b>Total groups showing elevated brain cancer:</b>	<b>423</b>
<b>Total studies showing at least one significantly elevated brain cancer</b>	<b>43</b>
<b>Total groups showing significantly elevated brain cancer:</b>	<b>153</b>
<b>Total studies showing at least one dose response relationship</b>	<b>28</b>
<b>Total groups showing dose-response trends of brain cancer:</b>	<b>78</b>
<b>Total groups showing significant dose-response trends <math>p \leq 0.1</math></b>	<b>64</b>
<b>Total groups showing significant dose-response trends <math>p \leq 0.05</math></b>	<b>48</b>

The studies showing dose-response relationships for EMF/EMR exposures are summarized in Table 6. Since the degrees of freedom ( $n-2$ ) are very small for dose-response trends it is appropriate to use a threshold of  $p \leq 0.1$ . Despite this the number of trends have  $p \leq 0.05$  and many have  $p < 0.01$ .

**Table 6: Studies showing dose-response relationships for EMR exposure and brain tumor:**

- Denver, United States, residential fields. Wertheimer and Leeper (1979)  
 Childhood ) Brain cancer is near 26% of all cancer.  
 All cancer) Dose related for children living at same address,  $p < 0.008$ .
- Electrical Occupations in Maryland, U.S. Lin et al. (1985)
 

	Glioma/Astrocytoma	Other Brain Tumors
Definite Exposure	2.15 (1.10-4.06)* n = 27	1.54 (0.68-3.38) n = 15
Probable exposure	1.95 (0.94-3.91) n = 21	1.30 (0.60-2.78) n = 19
Possible exposure	1.44 (1.00-1.95)* n = 128	0.94 (0.68-1.31) n = 87
No exposure	1.0 n = 323	1.0 n = 286
	Trend $p < 0.01$	Trend $p < 0.05$
- Eastern U.S. Electronic Industries Thomas et al. (1987)
 

		Duration Employed (yr)			
		Unexposed	<5	5-19	$\geq 20$
Astrocytic brain tumours	RR	1.0	3.3	7.6	10.4
Solder fume adjusted	RR	1.0	1.65	3.8	5.2
		(trend $p < 0.05$ )			
- United States, Meta Analysis Kheifets et al. (1995)
 

Pooled Dose-Response, Reference		RR = 1.0
Low		RR = 1.23 (1.06-1.42)
Middle		RR = 1.36 (1.11-1.68)
High		RR = 1.61 (1.28-2.04)
		Trend $p = 0.006$
- East Texas, Males Glioma Speers, Dobbins and Miller (1988)
 

		n=202
Electricity or electromagnetic fields	OR = 3.94 (1.52-10.20)*	Trend: $p < 0.01$
- Los Angeles County, Occupational exposure Preston-Martin et al. (1989)
 

		n=272
High exposure to electric and magnetic fields		
Glioma 0 years	OR = 1.0	
Glioma 0-5 years	OR = 1.4 (0.7-3.1)	
Glioma >5 years	OR = 1.8 (0.8-4.3)	Trend $p = 0.05$
Astrocytoma, >5 years empl.	OR = 4.3* (1.2-15.6)	Trend $p = 0.008$
- U.S., prenatal domestic appliances Savitz, John and Kleckner (1990)
 

Electric Blanket usage:		
Night duration use <8 hrs	OR = 1.5 (0.4-5.7)	n=3
Night Duration use = 8 hrs	OR = 3.1 (1.2-8.5)*	n=7
Night Duration use >8 hrs	OR = 4.5 (0.5-39.0)	n=1
(Assuming 4, 6, 8, 10 hours)	Trend $p = 0.019$	

- United States, 16 States (Mortality)  
adjusted for age & race

Loomis and Savitz (1990)

Dose-response relationship:

Exposure	Crude	Adjusted (age & race)
Possible only (Adj)	OR = 1.8* (1.4-2.3)	OR = 1.5* (1.1-1.9)
Unlikely (low) exposure (Adj)	OR = 1.3* (1.0-1.6)	OR = 1.2 (0.9-1.5)
Reference Control	OR = 1.0	OR = 1.0

- Los Angeles County, electrical industry

Mack et al. (1991)

Stratification from years worked in exposed situations:

Exposure Index 1, from Thomas et al. (1987)

Type of brain tumor	0	>0-5	>5-10	>10	Trend-p
All brain tumors	1.0	1.1 (0.6-2.0)	0.5 (0.1-2.0)	1.3 (0.3-3.0)	0.67
Glioma	1.0	1.1 (0.5-2.1)	0.4 (0.1-2.1)	1.7 (0.7-4.4)	0.21
Astrocytoma	1.0	1.1 (0.5-2.9)	0.4 (0.1-2.1)	10.3 (1.3-80.8)*	0.01**

Exposure Index 2, from Milham (1985)

Type of brain tumor	0	>0-5	>5-10	>10	Trend-p
All brain tumors	1.0	1.1 (0.6-2.2)	0.4 (0.1-1.7)	1.2 (0.5-2.8)	0.70
Glioma	1.0	1.2 (0.6-2.4)	0.4 (0.1-2.1)	1.4 (0.6-3.5)	0.32
Astrocytoma	1.0	1.3 (0.5-3.1)	0.4 (0.1-2.1)	4.6 (1.0-21.4)*	0.02*

- Sweden, Occupational exposure

Floderus et al. (1993)

Time Above 0.2mT,	<16%	17-23%	24-28%	≥29%	≥39%	Trend p
All brain tumors	1.0	1.3 (0.9-2.0)	1.3 (0.9-1.9)	1.5 (1.0-2.2)*	1.9 (1.2-3.1)*	0.005**
Astrocytoma III-IV	1.0	1.6 (1.0-2.6)*	1.6 (1.0-2.5)*	1.7 (1.1-2.8)*	2.1 (1.2-3.8)*	0.011*

Median Exposure	<0.11μT	0.12-0.16μT	≥0.17μT	≥0.20μT	
Astrocytoma I-II<40	1.0	0.9 (0.3-2.9)	2.7 (1.1-6.8)*	5.7 (1.9-16.7)*	0.035*
Adjusted for Benzene	1.0	1.0 (0.7-1.5)	1.4 (1.0-2.0)*	1.6 (1.0-2.5)*	0.051
Possible solvents	1.0	0.9 (0.5-1.9)	1.4 (0.9-2.2)	1.9 (0.8-4.5)	0.066

Median Exposure	≤0.15μT	0.20-0.28μT	≥0.29μT	≥0.41μT	
Study participants	1.0	1.1 (0.8-1.5)	1.2 (0.9-1.7)	1.4 (0.9-3.3)	0.003**
Study and Nonrespondents	1.0	1.0 (0.8-1.4)	1.2 (0.9-1.6)	1.3 (0.9-2.0)	0.05*
Age Specific ≤40					
Study participants	1.0	0.8 (0.4-1.8)	1.4 (0.7-3.0)	2.7 (1.0-7.8)*	0.094
Study and Nonrespondents	1.0	0.9 (0.5-1.9)	1.6 (0.8-3.3)	2.9 (1.1-7.7)	0.065

- Canada, Provincial Residential Electric Consumption (REC)  
Childhood brain cancer significantly increases with REC  
in a significant dose-response manner.

Kraut et al. (1994)

- Ontario, Quebec and France

Theriault et al. (1994)

Dose-response for the median, 90<sup>th</sup> %ile, with a strongly skewed distribution, using exposure weights of 15, 25 and 92.



## Ontario Hydro: Malignant Brain Cancer:

Trend p-value

Median: OR = 1.85 (0.53-6.49) >90<sup>th</sup> OR = 5.45 (0.59-50.59) p=0.036\*

## All Companies: Malignant Brain Cancer:

0-20 yrs Median: OR = 1.05 (0.20-5.35) >90<sup>th</sup> OR = 5.90 (0.37-94.91) p=0.065All Median: OR = 1.95 (0.98-3.86) >90<sup>th</sup> OR = 2.14 (0.80-5.72) p=0.44

## All Companies: Astrocytoma:

0-20 yrs Median: OR = 3.99 (0.72-22.0) >90<sup>th</sup> OR = 11.1\*(1.44-85.6) p=0.10All Median: OR = 3.69 (0.61-22.2) >90<sup>th</sup> OR = 28.48\*(1.76-461) p=0.02\*

## Cumulative exposure groups

Astrocytoma

Trend OR = 9.41\* (1.07-82.79)

- U.S. Electrical Workers, 1950-1988 Savitz and Loomis (1995)  
Measured field assessment and confounders.

## Cumulative exposures and duration windows:

## Total Exposure (RR)

0-<0.6	0.6-<1.2	1.2-<2	2-<4.3	≥4.3	Trend p
1.0	1.61 0.99-2.63	1.47 0.84-2.56	1.65 0.92-2.95	2.29*1.15-4.56	0.033*

## Past 2-10yrs

0	0-<0.2	0.2-<0.4	0.4-<0.7	≥0.7	Trend p
1.0	1.17 0.66-2.08	1.39 0.75-2.58	1.46 0.76-2.84	2.56*1.35-4.86	0.009**

## Past 10-20 yrs

0	0-<0.3	0.3-<0.5	0.5-<0.9	≥0.9	Trend p
1.0	1.76*1.07-2.91	1.26 0.69-2.29	1.47 0.76-2.84	1.63 0.92-2.90	0.44

## Past &gt;20

0	0-<0.4	0.4-<1.1	1.1-<2.0	≥2.0	Trend p
1.0	0.76 0.45-1.27	0.89 0.51-1.56	1.12 0.59-2.14	1.26 0.64-2.48	0.074

## Mortality

## Dose-response rates

RR per  $\mu$ T-yr

## 95%CI

Total Exposure

1.07\*

1.01-1.14

Past 2-10 years

1.94\*

1.34-2.81

Past 10-20 years

1.35\*

1.01-1.79

Past&gt;20 years

1.06

0.97-1.16

- U.S. electronics industry workers

Beall et al. (1996)

## Dose-response relationships:

Computer Programmers (&gt;10 yrs)

OR = 2.8 (1.1-7.0)\*

Trend p = 0.04

Engineering/Technical (&gt;10 yrs)

OR = 1.7 (1.0-3.0)\*

Trend p = 0.07

Glioma, All subjects, 5yr progrm.

OR = 3.9 (1.2-12.4)\*

Trend p = 0.08

- United States, office workers

Milham (1996)

Transformer fields

SIR = 389 (156-801)\*

N=410

Exposure trend p=0.0034

Employment period trend p&lt;0.05

- Ontario Hydro male employees (Adjusted ORs) Miller et al. (1996)

Brain Tumour	Mod. Field	OR = 1.27 (0.32-5.41)	Both show trends.
	High Field	OR = 1.33 (0.52 -10.8)	
Benign Brain Tumour	Mod. Field	OR = 5.38 (0.42-69.3)	
	High Field	OR = 5.64 (0.3-105)	

- France, electrical utility workers, ELF exposures Guenel et al. (1996)

Crude and adjusted on Magnetic Fields (MF), Socioeconomic Status (SES) and solvent exposures (SOL), given with exposure percentiles:

Percentiles:	Cases	OR Adj SES	OR Adj MF+SES	OR Adj. SES+SOL
<50	29	1.0	1.0	1.0
50-<75	22	2.47 (0.99-6.16)	2.51 (1.00-6.34)*	2.29 (0.89-5.94)
>75-90	8	1.43 (0.46-4.45)	1.43 (0.45-4.48)	1.43 (0.45-4.57)
>90	10	3.08 (1.08-8.74)*	2.83 (0.97-8.28)	2.97 (1.00-8.80)*

Adjusting for a 5-year latency gives the highest Odds ratios:

Cumulative Exposure V/m-years	Cases	OR	95%CI
<202	22	1.00	
202-274	20	3.43*	1.25-9.40
275-342	9	2.40	0.73-7.90
≥343	9	3.69*	1.10-12.43

Adjusting for 10-year latency gives a linear dose-response:

Cumulative Exposure V/m-years	Cases	OR	95%CI
<166	22	1.00	
166-229	14	1.67	0.67-4.19
230-294	9	1.79	0.60-5.36
≥295	7	2.15	0.63-7.26

Trend p = 0.013

- Children in Los Angeles (1996b) Preston-Martin et al.

Dose-response relationship:

All years Reference <1mG	OR = 1.0	
>2mG	OR = 1.2 (0.5-2.8)	n=16
>2.5mG	OR = 1.4 (0.5-3.8)	n=13
>3mG	OR = 1.7 (0.6-5.0)	n=12
Trend p = 0.036		

- Norway Tynes and Haldorsen (1997)
- |          |               |                    |               |        |
|----------|---------------|--------------------|---------------|--------|
| Children | <0.05 $\mu$ T | 0.05-<0.14 $\mu$ T | >0.14 $\mu$ T | n=10   |
| RR =     | 1.0           | 2.6 (0.5-12.0)     | 2.3 (0.8-6.6) | p=0.07 |

- Sweden, Electrical Occupations Rodvall et al. (1998)

Dose-response for groups with >10 cases:

Estimated daily Mean:	<0.2 $\mu$ T	0.2-0.4 $\mu$ T	>0.4 $\mu$ T	>0.4 $\mu$ T for ≥5yrs
Glioma (Mean)	1.0	1.1 (0.4-2.7)	1.9 (0.8-5.0)	1.8 (0.7-5.1)

Estimated daily Median:	<0.12 $\mu$ T	0.12-0.19 $\mu$ T	>0.19 $\mu$ T	>0.19 $\mu$ T for $\geq$ 5yrs
Glioma (Median)	1.0	1.1 (0.5-2.6)	1.4 (0.5-3.6)	1.5 (0.6-4.1)

## Dose-response

Estimated daily Mean:	<0.2 $\mu$ T	0.2-0.4 $\mu$ T	>0.4 $\mu$ T
Glioma (Mean)	1.0	1.3 (0.07-2.4)	1.3 (0.5-3.2)
Estimated daily Median:	<0.12 $\mu$ T	0.12-0.19 $\mu$ T	>0.19 $\mu$ T
Glioma (Median)	1.0	1.9 (1.0-3.5)	1.1 (0.5-2.6)

- United States Utility Workers 5 studies combined  
RR per 10  $\mu$ T-years RR = 1.12 (0.98-1.28) Kheifets et al. (1999)
- Swedish cohort study of ELF exposures Floderus, Stenlund and Persson (1999)  
Occupational Exposure of Males:  
1971-1977 Middle Exp 0.084-0.115 $\mu$ T High Exp  $\geq$ 0.116 $\mu$ T  
Astrocytoma III-IV RR = 1.1 (0.9-1.4) RR = 1.2 (1.0-1.5)\*  
1971-1984 Middle Exp 0.084-0.115 $\mu$ T High Exp  $\geq$ 0.116 $\mu$ T  
Astrocytoma III-IV RR = 1.2 (1.1-1.4)\* RR = 1.3 (1.2-1.5)\*
- United States Electric Utility Workers Savitz et al. (2000)  
Reference OR = 1.0  
Cumulative exposure OR = 1.8 (0.7-4.7)  
Average exposure OR = 2.5 (1.0-6.3)\*

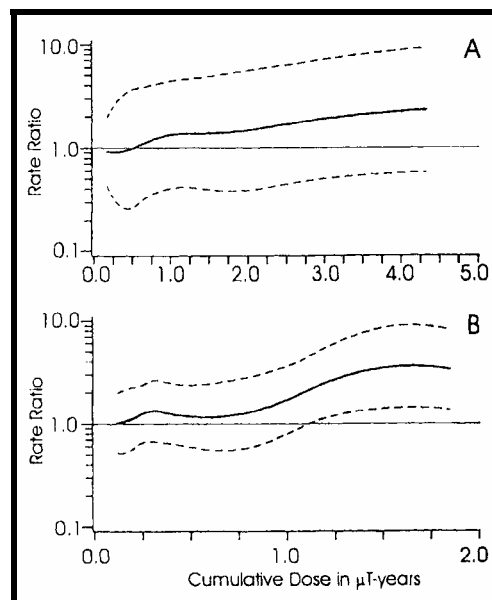


Figure 18: Brain cancer increases from refined case-cohort job-exposure matrix in the US Utility Worker Mortality Study 1950-1988, Savitz et al. (2000). Cumulative exposure over entire career with A: a 2-year lag; B: 2-10 years in the past.

- Cell phone users in Denmark Johansen et al. (2001)  
Duration of digital subscription <1 yr 1-2yrs  $\geq$ 3 yrs  
Relative to reference group SIR 0.7 0.9 1.2  
Relative to <1 yr group RR 1.0 1.29 1.71

- San Francisco, Sutra Tower (FM/TV) Cherry (2002)  
Children < 21 yrs Brain Cancer

Ring (km)	RR	95%CI	
0.1-1	15.5	3.14-76.8	
1-2	7.8	2.1-30.9	
2-3	3.3	0.84-13.4	
3-4	3.2	0.85-12.1	
4-5	3.07	0.81-11.6	Trend p-value=0.03
>5	1.00		Log/Lin Trendp<0.001

- Canadian Electrical Workers Villeneuve et al.(2002)

	Highest average exposure <0.3 $\mu$ T	$\geq 0.3\mu$ T	$\geq 0.6\mu$ T
All Brain Cancer OR(adj)	1.0	1.12 (0.83-1.51)	1.33 (0.75-2.36)
Glioblastoma multiforme	1.0	1.48 (0.89-2.47)	5.36 (1.16-24.78)
Other Brain Cancers	1.0	1.10 (0.58-2.09)	1.58 (0.56-4.50)
	Average exposure <0.3 $\mu$ T	$\geq 0.3\mu$ T-<0.6 $\mu$ T	$\geq 0.6\mu$ T
All Brain Cancer OR(adj)	1.0	1.13 (0.72-1.79)	1.50 (0.69-3.28)
Glioblastoma multiforme	1.0	1.99 (0.83-4.81)	12.59 (1.50-105.6)

- Cell phone users in Finland Auvinen et al. (2002)  
Significantly elevated brain cancer and salivary gland cancers from analogue phone usage.

Trends of OR for years of usage are:		
All Brain Cancers,	Analogue Phones	1.2* (1.0-1.3)
	Total Phones	1.1* (1.0-1.3)
Glioma	Analogue Phones	1.2* (1.1-1.5)
	Total Phones	1.2* (1.0-1.4)
Other Brain cancers	Analogue Phones	1.1 (0.8-1.4)
	Total Phones	1.1 (0.8-1.4)
Salivary gland cancers	Analogue Phones	1.3 (0.7-2.5)
	Digital Phones	1.5 (0.2-11.9)
	Total Phones	1.3 (0.7-2.6)

### Summary of Brain Cancer studies:

The epidemiological studies on EMR associated brain cancer include 96 studies of over 400 separate groups with elevated brain cancer from EMR exposure from across the spectrum. Of the 423 groups, 153 show significant increases, 78 show dose response relationships and 48 of these are statistically significant. From acknowledged RF/MW exposure there are 35 groups, 19 with significant increases, 8 with dose responses, of which 6 are significant. This is strongly backed by evidence of genotoxicity. This evidence is more than sufficient, using the Bradford-Hill guidance, Hill (1965), to conclude that there is a causal relationship between EMR exposure across the spectrum and brain tumour incidence and mortality

Significant increases in brain cancer incidence or mortality are shown in welders, equipment repairers, microwave repairers, utility workers, telephone industry workers, amateur radio operators, military personnel exposed to radio and radar, commercial and

air force pilots and aircrew, computer users, children living near broadcast towers and high voltage powerlines and cell phone users.

### **Cell phones and Brain tumours:**

Analogue cell phones use FM radio signals while digital cell phones use pulsed microwaves that are very similar to radar. The analogue phones expose the user's head to much higher intensities of microwaves than the more modern digital phones. The way the information is encoded in the pulsed differs but it is the pulsing action that is likely to enhance the biological effects. Since FM exposed populations show significant increases and significant dose-response increases in brain tumour at very low exposure levels, Cherry (2002a), and since cell phone produce far high mean exposures and the same neurological effects in a dose response manner, Mild et al. (1998), then analogue cell phones are highly likely to produced significant increases in brain cancer and degenerative neurological diseases.

Dr Andrew Davidson, an Oncologist in Western Australia, Davidson (1998), has noted a parallel increase in diagnosed brain tumours with the rising use of mobile phones. In a comment Dr Bruce Hocking refers to Rothman et al. (1996) who compared the mortality rates during 1994 of portable (hand-held) phone users and mobile (Bag) phone users. Dr Hocking quotes the results of  $RR = 0.86$  to show that mobile phone users have a lower mortality rate. Actually Rothman et al. have deliberately reversed the ratio so that people will take the conclusion that Dr Hocking has drawn by reporting the rate of portable phone use over mobile phone use. When it is corrected, and mobile phone use is compared with portable phone use, for all users and for male users, mobile phone users have significantly higher mortality rates than portable phone users.

Table 7: Comparative mortality rates between mobile (Bag) phone users and portable (hand-held) phone users in the United States for 1994, Rothman et al. (1996).

Group	RR	95%CI	p-value
For Men	1.40	1.06 - 1.86	0.017
For Women	1.52	0.78 - 2.95	0.31
All People	1.38	1.07 - 1.79	0.013

Hardell et al. (1999) found no overall increase in brain cancer risk for mobile phone users compared with the general population. However they did find a marginally insignificant increase in a particular type of tumour at the position and side of the head that received the highest exposure from the mobile phone, based on 209 cases and 425 controls. Left side  $OR = 2.4$ , 95%CI: 0.52-10.9 and Right Side  $OR = 2.45$ , 95%CI: 0.78 - 7.76. They found a slightly higher rate for the digital GSM phones compared with the analogue NMT phones.

Dr George Carlo, former chairman of Wireless Technology Research (WTR), the industry funded research body in the U.S., reported that the studies they had funded had reported similar results to those in Sweden,

Digital phones are like radar and radar exposure has been shown to significantly increase brain tumour, Szmigielski (1996). Tice et al. (1999) reported that every cell phone tested in their U.S. laboratory caused chromosome aberrations in a dose response manner up to a 3-fold increase. Phillips et al. (1998), Maes and Verschaeve and Maes (1998) observed

significant DNA damage from a range of digital cell phone signals. Phillips et al. used exposures of 1.2 and 13 $\mu$ W/cm<sup>2</sup>.

The largest and most careful case-control cell phone usage and brain cancer studies have been carried out in Sweden, Hardell et al. (1999, 2000, 2001, 2002a,b). Initially small case samples (n=270) showed elevated brain cancer from using an analogue mobile phone. When the results included more cases and adjusted the results for Xray and therapy exposures, the incidence of Brain Cancer on the side of the head that was exposed was significantly elevated, OR = 2.62 (1.02-6.71). The study group was significantly expanded to include 1429 cases. Using a cell phone for longer than a year raised the risk of Brain Cancer, OR = 1.26 (1.02-1.56). For longer latency periods, > 5 years gave OR = 1.35 (1.03-1.77) and > 10 years OR = 1.77 (1.09-2.86). For the side of the head the phone exposed OR = 2.50 (1.2-4.88).

For Acoustic Neuromas among analogue phone users OR =3.27 (1.67-6.43). The final study involved only patients with Astrocytomas (n=414). For analogue phone use OR = 1.29 (0.87-1.90) and digital phone use OR = 1.1 (0.81-1.53). When the side of the head where the phone was used was considered, for Analogue phone OR = 1.85 (1.12-3.39) for all Brain Cancers and OR = 1.95 (1.12-3.39) for Astrocytomas. For digital and cordless phones, the risk of side of head astrocytomas was OR= 1.59 (0.98-2.58) and OR= 1.70 (1.06-2.74) respectively, Hardell et al. (2002a). For astrocytomas in the temporal or occipital areas, OR=9.00 (1.14-71.0) based on 12 cases and 5 controls, Hardell et al. (2002b).

## **Summary and Conclusions:**

Has a very sensitive electromagnetic organ. Since the published research shows that electromagnetic fields and radiation significantly enhance neurological responses by the brain acute exposure to mobile telephones. And there's a large body of evidence showing that people who live and work in electromagnetic fields have a significantly higher rate of neurological disorders, including Motor Neuron Disease, Alzheimer's disease, Parkinson's disease, and enhance epileptic fits. There is also robust evidence that there is a causal relationship between sleep disturbance, depression, suicide and brain cancer from chronic exposure to electromagnetic fields and radiation. The symptoms of radiofrequency or microwave syndrome must not be dismissed as simply subjective reactions. They are real and biologically sensible responses of an electromagnetic organ to electromagnetic interference.

All of these symptoms and disease rates are being enhanced by electromagnetic fields of homes, radiofrequency fields and radio and TV towers and the extensive installation of cell sites and the use of cellular telephones.

The causal association of neurological diseases and mortality from residential exposures to electromagnetic fields for about one million times higher than the Schumann Resonance signal, and cell phone exposures of one billion times higher than Schumann Resonance signal, there is highly scientifically sensible and well-established by multiple independent epidemiological studies.

Therefore public health protection standards should be set at 10nW/cm<sup>2</sup> to significantly reduce the risk rate in the public from the well identified and serious neurological symptoms, diseases and mortality rates.

## References:

- Ahlbom, A., 2001: "Neurodegenerative diseases, suicide and depressive symptoms in relation to EMF". Bioelectromagnetics Supplement 5: S132-S143.
- Adey, W.R., 1975: "Introduction: Effects of electromagnetic radiation on the nervous system". Annals N.Y. Acad. Sci. 247: 15-20.
- Adey, W.R., 1979: "Neurophysiologic effects of Radiofrequency and Microwave Radiation". Bull NY Acad Med 55(11): 1079-93.
- Adey, W.R., 1980: "Frequency and Power windowing in tissue interactions with weak electromagnetic fields". Proc. IEEE, 68:119-125.
- Adey, W.R., 1980: "Tissue Interactions with nonionizing electromagnetic fields". Physiological Reviews 61(2): 435-514.
- Adey, W.R., 1993: "Electromagnetics in Biology and Medicine". In Modern Radio Science (Hiroshi Matsumoto ed). Oxford, England, Oxford University Press, 227-245.
- Ahissar, E., Haidarliu, S. and Zacksenhouse, M., 1997: "Decoding temporally encoded sensory input by cortical oscillations and thalamic phase comparators". Proc Nat Acad Sci USA 94:11633-11638.
- Ahuja YR, Bhargava A, Sircar S, Rizwani W, Lima S, Devadas AH, Bhargava SC. "Comet assay to evaluate DNA damage caused by magnetic fields. In: Proceedings of the International Conference on Electromagnetic Interference and Compatibility, India Hyderabad, December 1997: 272-276.
- Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Molecular Biology of the cell, 3rd edition, New York, Garland Publishing, 1994.
- Altpeter ES, Krebs Th, Pfluger DH, von Kanel J, Blattmann R, Emmenegger D, Cloetta B, Rogger U, Gerber H, Manz B, Coray R, Bauman R, Staerk K, Griot Ch, Abelin Th. Study of health effects of Short-wave Transmitter Station of Schwarzenburg, Berne, Switzerland. University of Berne, Institute for Social and Preventative Medicine, August (1995).
- Altpeter ES, Sprenger K, Madarasz K, Abelin Th., 1997: "Do radiofrequency electromagnetic fields cause sleep disorders?" In: Proceedings of the IAE meeting, Munster, Germany, Abst. No. 351.
- Armstrong B, Theriault G, Guenel P, Deadman J, Goldberg M, Heroux P. Am J Epidemiol 140(9):805-820 (1994).
- Arnetz, B.B. and Berg, M., 1996: "Melatonin and Andrenocorticotrophic Hormone levels in video display unit workers during work and leisure. J Occup Med 38(11): 1108-1110.
- Auvinen, A., Hietanen, M., Luukkonen, R. and Koskela, R-S, 2002: "Brain Tumours and Salivary Gland Cancers among cellular telephone users". Epidemiology 13: 356-359.
- Band PR, Le ND, Fang R, Deschamps R, Coldman A, Gallagher RP, Moody J. Cohort study of Air Canada pilots: mortality incidence and leukaemia risk. Am J Epidemiol 143(2):137-143 (1996).
- Band PR, Spinelli JJ, Ng VT, Moody J, Gallagher RP. Mortality and cancer incidence in a cohort of commercial airline pilots. Aviat Space Environ Med 61(4):299-302 (1990).

- Balcer-Kubiczek EK. Experimental studies of electromagnetic field-induced carcinogenesis in cultured mammalian cells. In: On the nature of electromagnetic field interactions with biological systems (Allan H Frey ed). Austin Texas, R.G. Landes Co. (1995)
- Baranski S, Czerski P. Biological effects of microwaves. Stroudsburg, Pennsylvania: Dowden, Hutchison and Ross Inc, 1976.
- Bawin, S.M. and Adey, W.R., 1976: "Sensitivity of calcium binding in cerebral tissue to weak electric fields oscillating at low frequency". *Proc. Natl. Acad. Sci. USA*, 73: 1999-2003.
- Bawin SM, Gavalas-Medici R, Adey WR., 1973: "Effects of modulated very high frequency fields on specific brain rhythms in cats". *Brain Res* 58: 365-384.
- Bawin SM, Kaczmarek LK, Adey WR. Effects of modulated VHF fields on the central nervous system. *Ann NY Acad Sci* 247:74-81 (1975).
- Beale IL, Pearce NE, Conroy DM, Hemming MA, Murrell KA. Psychological effects of chronic exposure to 50 Hz magnetic fields in human living near extra-high-voltage transmission lines. *Bioelectromagnetics* 18(8):584-594 (1997).
- Beall C, Delzell E, Cole P, Brill I. Brain Tumors among electronics Industry Workers. *Epidemiology* 7(2): 125-130 (1996).
- Blackman, C.F., Benane, S.G., Elliott, D.J., and Pollock, M.M., 1988: "Influence of Electromagnetic Fields on the Efflux of Calcium Ions from Brain Tissue in Vitro: A Three-Model Analysis Consistent with the Frequency Response up to 510 Hz". *Bioelectromagnetics*, 9:215-227.
- Blackman, C.F., Kinney, L.S., House, D.E., and Joines, W.T., 1989: "Multiple power-density windows and their possible origin". *Bioelectromagnetics*, 10: 115-128.
- Blackman, C.F., 1990: "ELF effects on calcium homeostasis". In "Extremely low frequency electromagnetic fields: The question of cancer", BW Wilson, RG Stevens, LE Anderson Eds, Publ. Battelle Press Columbus: 1990; 187-208.
- Blackman, C.F., Benane, S.G., and House, D.E., 1991: "The influence of temperature during electric- and magnetic-field induced alteration of calcium-ion release from in vitro brain tissue". *Bioelectromagnetics*, 12: 173-182.
- Blackman CF, Benane SG, Elliott DJ, Pollock MM. Influence of Electromagnetic Fields on the Efflux of Calcium Ions from Brain Tissue in Vitro: A Three-Model Analysis Consistent with the Frequency Response up to 510 Hz. *Bioelectromagnetics* 9:215-227 (1988).
- Blackman CF, Kinney LS, House DE, Joines WT. Multiple power-density windows and their possible origin. *Bioelectromagnetics* 10: 115-128 (1989).
- Blackman CF. ELF effects on calcium homeostasis. In *Extremely low frequency electromagnetic fields: The question of cancer* (BW Wilson, RG Stevens, LE Anderson eds) Columbus, Battelle Press: 1990; 187-208.
- Borbely, AA, Huber, R, Graf, T, Fuchs, B, Gallmann, E, Achermann, P, 1999: Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram. *Neurosci Lett* 275(3):207-210.
- Burch JB, Reif JS, Pittratt CA, Keefe TJ, Yost MG. Cellular telephone use and excretion of a urinary melatonin metabolite. In: *Annual review of Research in Biological Effects of*



- electric and magnetic fields from the generation, delivery and use of electricity, San Diego, CA, Nov. 9-13, 1997: P-52.
- Braune S, Wrocklage C, Raczek J, Gailus T, Lucking CH. Resting blood pressure increase during exposure to a radio-frequency electromagnetic field. *Lancet* 351:1857-1858 (1998).
- Brueve R, Feldmane G, Heisele O, Volrate A, Balodis V. Several immune system functions of the residents from territories exposed to pulse radio-frequency radiation. Presented to the Annual Conference of the ISEE and ISEA, Boston Massachusetts July 1998.
- Burch, J.B., Reif, J.S., Pittrat, C.A., Keefe, T.J. and Yost, M.G., 1997: "Cellular telephone use and excretion of a urinary melatonin metabolite". In: Annual review of Research in Biological Effects of electric and magnetic fields from the generation, delivery and use of electricity, San Diego, CA, Nov. 9-13, P-52.
- Burch, J.B., Reif, J.S., Yost, M.G., Keefe, T.J. and Pittrat, C.A., 1998: "Nocturnal excretion of urinary melatonin metabolite among utility workers". *Scand J Work Environ Health* 24(3): 183-189.
- Burch, J.B., Reif, J.S., Yost, M.G., Keefe, T.J. and Pittrat, C.A., 1999a: "Reduced excretion of a melatonin metabolite among workers exposed to 60 Hz magnetic fields" *Am J Epidemiology* 150(1): 27-36.
- Burch, J.B., Reif, J.S. and Yost, M.G., 1999b: "Geomagnetic disturbances are associated with reduced nocturnal excretion of melatonin metabolite in humans". *Neurosci Lett* 266(3):209-212.
- Burch, J.B., Reif, J.S., Noonan, C.W. and Yost, M.G., 2000: "Melatonin metabolite levels in workers exposed to 60-Hz magnetic fields: work in substations and with 3-phase conductors". *J of Occupational and Environmental Medicine*, 42(2): 136-142.
- Burch JB, Reif JS, Yost MG, Keefe TJ, Pittrat CA. Nocturnal excretion of urinary melatonin metabolite among utility workers. *Scand J Work Environ Health* 24(3): 183-189 (1998).
- Burch JB, Reif JS, Yost MG. Geomagnetic disturbances are associated with reduced nocturnal excretion of melatonin metabolite in humans. *Neurosci Lett* 266(3):209-212 (1999).
- Cherry, N.J., 2002: "Schumann Resonances, a plausible biophysical mechanism for the human health effects of Solar/Geomagnetic Activity". *Natural Hazards* 56: 279-331.
- Cocco P, Heineman EF, Docemeci M. Occupational risk factors for cancer of the central nervous system (CNS) among US women. *Am J Ind Med* 36(1):70-74 (1999).
- Dasdag, S, Ketani, MA, Akdag, Z, Ersay, AR, Sar,i I, Demirtas ,OC, Celik, MS, 1999: Whole-body microwave exposure emitted by cellular phones and testicular function of rats. *Urol Res* 27(3):219-223.
- Davanipour Z, Sobel E, Bowman JD, Qian Z, Will AD. Amyotrophic Lateral Sclerosis and occupational exposure to electromagnetic fields. *Bioelectromagnetics* 18: 28-35 (1997).
- Davidson, J.A., 1998: "Brain tumour and mobile phones?". *Medical Journal of Australia* 12(1):48.
- Davis, S., 1997: "Weak residential Magnetic Fields affect Melatonin in Humans", *Microwave News*, Nov/Dec 1997.
- Davis, S., Mirick, D.K. and Stevens, R.G., 2002: "Residential magnetic fields and the risk of breast

- cancer". *Am J Epidemiology* 155(5): 446-454.
- Deapen DM, Henderson BE. A case-control study of Amyotrophic Lateral Sclerosis. *Am. J. Epidemiol* 123(5): 790-799 (1986).
- Deroche m. Etude de perturbations biologiques chez les techniciens O.R.T.F. dans certains champs electromagnetiques de haute frequence. *Arch Mal Prof* 32:679-683 (1971).
- de Seze R, Fabbro-Peray P, Miro L. GSM radiocellular telephones do not disturb the secretion of antipituitary hormones in humans. *Bioelectromagnetics* 19(5): 271-278 (1999).
- Dockerty JD, Elwood JM, Skegg DC, Herbison GP. Electromagnetic field exposures and childhood cancers in New Zealand. *Cancer Causes and Control* 9(3):299-309 (1998).
- Dolk H, Shaddick G, Walls P, Grundy C, Thakrar B, Kleinschmidt I, Elliott P. Cancer incidence near radio and television transmitters in Great Britain, I Sutton Coldfield transmitter. *Am J Epidemiol* 145(1):1-9 (1997).
- Dolk H, Elliott P, Shaddick G, Walls P, Grundy C, Thakrar B. Cancer incidence near radio and television transmitters in Great Britain, II All high power transmitters. *Am J Epidemiol* 145(1):10-17 (1997).
- Donnellan M, McKenzie DR, French PW, 1997: Effects of exposure to electromagnetic radiation at 835 MHz on growth, morphology and secretory characteristics of a mast cell analogue, RBL-2H3. *Cell Biol Int* 21:427-439.
- Dosemeci M, Blair A. Occupational Cancer Mortality Among Women Employed in the Telephone Industry. *J Occup Med* 36 (11):1204-1209 (1994).
- Eulitz, C, Ullsperger, P, Freude, G, Elbert ,T, 1998: Mobile phones modulate response patterns of human brain activity. *Neuroreport* 9(14):3229-3232.
- Fanelli C, Coppola S, Barone R, Colussi C, Gualandi G, Volpe P, Ghibelli L. Magnetic fields increase cell survival by inhibiting apoptosis via modulation of  $Ca^{2+}$  influx. *FASEB Journal* 13(1): 95-102 (1999).
- Fear NT, Roman E, Carpenter LM, Newton R, Bull D. Cancer in electrical workers: an analysis of cancer registrations in England, 1981-1987. *Br J Cancer* 73(7): 935-939 (1996).
- Fesenko, EE, Makar, VR, Novoselova, EG, Sadovnikov, VB, 1999: Microwaves and cellular immunity. I. Effect of whole body microwave irradiation on tumor necrosis factor production in mouse cells. *Bioelectrochem Bioenerg* 49(1):29-35.
- Feychting M, Pedersen NL, Svedberg P, Floderus B, Gatz M. Dementia and occupational exposure to magnetic fields. *Scand J Work Environ Health* 24(1): 46-53 (1998).
- Feychting M, Ahlbom A. Magnetic fields and cancer in children residing near Swedish High-voltage power lines. *Am J Epidemiol* 138 (7):467-481 (1993).
- Feychting M, Forssen U, Floderus B. Occupational and residential magnetic field exposure and leukemia and central nervous system tumors. *Epidemiology* 8(4):384-389 (1997).
- Feychting M, Schulgen G, Olsen JH, Ahlbom A. Magnetic fields and childhood cancer- pooled analysis of two Scandinavian studies. *Europ J Cancer* 31A (12): 2035-2039 (1995).

- Floderus B, Persson T, Stenlund C, Wennberg A, Ost A, Knave B Occupational exposure to electromagnetic fields in relation to leukemia and brain tumors: a case-control study in Sweden. *Cancer Causes Control* 4(5):465-76 (1993).
- Forman, S.A., Holmes, C.K., McManamon, T.V., and Wedding, W.R., 1982: "Physiological Symptoms and Intermittent Hypertension following acute microwave exposure". *J. of Occup. Med.* 24(11): 932-934.
- Fraumeni JF, Devesa SS, Hoover RN, Kinlen LJ. Epidemiology of cancer. In: *Cancer: Principles and Practice of Oncology*, 4th edition, (Vincent T De Vita, Jr, Samuel Hellman, Steven A Rosenberg, ed), Philadelphia, J.B. Lippincott Co., 1993; 150-181.
- Freude, G, Ullsperger, P, Eggert ,S, Ruppe, I, 1998: Effects of microwaves emitted by cellular phones on human slow brain potentials. *Bioelectromagnetics* 19(6):384-387.
- French PW, Donnellan M, McKenzie DR, 1997: Electromagnetic radiation at 835 MHz changes the morphology and inhibits proliferation of a human astrocytoma cell line. *Bioelectrochem Bioenerg* 43:13-18.
- Freude, G, Ullsperger, P, Eggert, S, Ruppe, I, 2000: Microwaves emitted by cellular telephones affect human slow brain potentials. *Eur J Appl Physiol* 81(1-2):18-27.
- Frey, A.H., 1995: "An integration of the data on mechanisms with particular reference to cancer", Chapter 2 in "On the Nature of electromagnetic Field Interactions with Biological Systems", Ed A.H. Frey, Publ. R.G. Landes Co. Medical Intelligence Unit, Austin, Texas.
- Frey AH. Headaches from cellular telephones: are they real and what are the impacts. *Environ Health Perspect* 106(3):101-103 (1998).
- Fritze K, Wiessner C, Kuster N, Sommer C, Gass P, Hermann DM, Kiessling M, Hossmann KA, 1997: Effect of global system for mobile communication microwave exposure on the genomic response of the rat brain. *Neuroscience* 81(3):627-639.
- Gavalas-Medici R, Day-Magdaleno SR. Extremely low frequency weak electric fields affect schedule-controlled behaviour of monkeys. *Nature* 261:256-258 (1976)
- Goswami PC, Albee LD, Parsian AJ, Baty JD, Moros EG, Pickard WF, Roti Roti JL, Hunt CR. Proto-oncogene mRNA levels and activities of multiple transcription factors in C3H 10T 1/2 murine embryonic fibroblasts exposed to 835.62 and 847.74 MHz cellular telephone communication frequency radiation. *Radiat Res* 151(3): 300-309 (1999).
- Goldsmith JR. Incorporation of epidemiological findings into radiation protection standards. *Public Health Rev* 19:19-34 (1991/92).
- Goldsmith, JR. Epidemiological Evidence of Radiofrequency Radiation (Microwave) Effects on Health in Military, Broadcasting, and Occupational Studies. *Int J Occup Environ Health* 1: 47-57 (1995).
- Goldsmith JR. Epidemiologic evidence relevant to radar (Microwave) effects. *Environ Health Perspect* 105 (Suppl 6): 1579-1587 (1997).
- Gordon, ZV. Problems of industrial hygien and the biological effects of electromagnetic superhigh frequency fields. [In Russian], Moscow Medicina. (1966). English Translation in NASA Rep. TT-F-633, 1976.
- Graham C, Cook MR. Human sleep in 60 Hz magnetic fields. *Bioelectromagnetics* 20: 277-283 (1999).

- Graham, C., Cook, M.R., Cohen, H.D. and Gerkovich, M.M., 1994: "A dose response study of human exposure to 60Hz electric and magnetic fields". *Bioelectromagnetics* 15: 447-463.
- Graham, C., Cook, M.R., Sastre, A., Riffle, D.W. and Gerkovich, M.M., 2000: "Multi-night exposure to 60 Hz magnetic fields: effects on melatonin and its enzymatic metabolite". *J Pineal Res* 28(1): 1-8.
- Grayson JK. Radiation Exposure, Socioeconomic Status, and Brain Tumour Risk in the US Air Force: A nested Case-Control Study. *Am J Epidemiol* 143 (5), 480-486 (1996).
- Grayson JK, Lyons TJ. Cancer incidence in the United States Air Force. *Aviat Space Environ Med* 67(2):101-104 (1996).
- Green LM, Miller AB, Agnew DA, Greenberg ML, Li J, Villeneuve PJ, Tibshirani R. Childhood leukaemia and personal monitoring of residential exposures to electric and magnetic fields in Ontario, Canada. *Cancer Causes Control* 10(3):233-243 (1999).
- Guberan E, Usel M, Tissot R, Sweetnam PM. Disability, mortality and incidence of cancer among Geneva painters and electricians: a historical prospective study. *Br J Ind Med* 46:16-23 (1989).
- Guenel P, Nicolau J, Imbernon E, Chevalier A, Goldberg M. Exposure to electric field and incidence of leukemia, brain tumors, and other cancers among French electric utility workers. *Am J Epidemiol* 144(12):1107-1121(1996).
- Hamer, J.R., 1965: Biological entrainment of the human brain by low frequency radiation". NSL 65-199, Northrop Space Labs.
- Hamer, J.R., 1969: "Effects of low level, low frequency electric fields on time judgement". Fifth Intern. Biometeorological Congress, Montreaux, Switzerland.
- Hammett and Edison Inc. Engineering analysis of radio frequency exposure conditions with addition of digital TV channels. Prepared for Sutra Tower Inc., San Francisco, California, January 3, 1997.
- Hardell L, Nasman A, Pahlson A, Hallquist A, Hansson Mild K, Use of cellular telephones and the risk of brain tumours: A case-control study. *Int J Oncology*, 15(1): 113-116 (1999).
- Hardell, L, Reizenstein, J, Johansson, B, Gertzen, H, Mild, KH, 1999: Angiosarcoma of the scalp and use of a cordless (portable) telephone. *Epidemiology* 10(6):785-786.
- Hardell, L, Nasman, A, Hallquist, A, 2000: "Case-control study of radiology work, medical X-ray investigations and use of cellular telephones as risk factors". *J of General Medicine* [www.medscape.com/Medscape/GeneralMedicine/journal/2000/v02.n03/](http://www.medscape.com/Medscape/GeneralMedicine/journal/2000/v02.n03/)>
- Hardell, L. Hansson Mild, K.,H., Hallquist, A., Carlberg, M., Pahlson, A., Lilja, A. and Larsson, I., 2001: "Swedish study on use of cellular and cordless telephones and the risk for brain tumours". Conference Mobile Telephones and Health – The Latest Developments, London June 6-7, 2001
- Hardell, L., Hallquist, A., Hansson Mild, K., Carlberg, M., Pahlson, A. and Lilja A., 2002a: "Cellular and Cordless Telephones and the Risk for Brain Tumors". *European Journal of Cancer Prevention*. 11(4): 377-386.

- Hardell, L., Hansson Mild. K., and Carlberg, M., 2002b: "Use of Cellular Telephones and the Risk for Astrocytomas" unpublished manuscript, In Press, October 2002, International Journal of Radiation Biology.
- Heineman EF, Gao YT, Dosemeci M, McLaughlin JK. Occupational risk factors for brain tumors among women in Shanghai, China. *J Occup Environ Med* 37(3): 288-293 (1995).
- Heller JH, Teixeira-Pinto AA. A new physical method of creating chromosome aberrations. *Nature*, 183 (4665): 905-906 (1959).
- Hill A.B., 1965: "The environment and disease: Association or causation?". *Proc Royal Soc Med* 58: 295-300.
- Hladky, A, Musil, J, Roth, Z, Urban, P, Blazkova, V, 1999: Acute effects of using a mobile phone on CNS functions. *Cent Eur J Public Health* 7(4):165-167.
- Hocking B, Preliminary report: Symptoms associated with mobile phone use. *Occup Med* 48(6): 357-360 (1998).
- Hocking B, Gordon IR, Grain HL, Hatfield GE. Cancer incidence and mortality and proximity to TV towers. *Med J Australia* 165: 601-605 (1996).
- Irvine D, Davies DM. The mortality of British Airways pilots, 1966-1989: a proportional mortality study. *Aviat Space Environ Med* 63(4):276-279 (1992).
- Ivaschuk OI, Jones RA, Ishida-Jones T, Haggren Q, Adey WR and Phillips JL. Exposure of nerve growth factor-treated PC12 rat pheochromocytoma cells to a modulated radiofrequency field at 836.55 MHz: effects on c-jun and c-fos expression. *Bioelectromagnetics* 18(3): 223-229 (1997).
- Jacobson, C.B., 1969: Progress report on SCC 31732, (Cytogenic analysis of blood from the staff at the U.S. Embassy in Moscow), George Washington University, Reproductive Genetics Unit, Dept. of Obstetrics and Gynecology, February 4, 1969.
- Johansen C, Olsen JH. Risk of cancer among Danish utility workers - a nationwide cohort study. *Am J Epidemiol* 147(6):548-555(1998).
- Johansen C, Koch-Hendriksen N, Rasmussen S, Jørgen OH. Multiple Sclerosis among utility workers. *Neurology* 52(6): 1279-1282 (1999).
- Johansen, C., 2000: "Exposure to electromagnetic fields and risk of central nervous system disease in utility workers". *Epidemiology* 11(5): 539-543.
- Johansen, C., Boice, J.D., McLaughlin, J.K., and Olsen, J., 2001: "Cellular telephones and cancer-a nationwide cohort study in Denmark". *J Nat Cancer Inst* 93(3): 203-207.
- Johnson-Liakouris AJ. Radiofrequency (RF) Sickness in the Lilienfeld Study: an effect of modulated microwaves. *Arch Environ Health* 53(3):236-238 (1998).
- Jones IF. A study of the propagation of wavelengths between three and eight meters. *Proc Inst Radio Eng* 21(3): 349-386 (1933).
- Juutilainen, J., Stevens, R.G., Anderson, L.E., Hansen, N.H., Kilpelainen, M., Laitinen, J.T., Sobel, E. and Wilson, B.W., 2000: "Nocturnal 6-hydroxymelatonin sulphate excretion in female workers exposed to magnetic fields". *J Pineal Res* 28(2): 97-104.

- Juutilainen J, Laara E, Pukkala E. Incidence of leukaemia and brain tumours in Finnish workers exposed to ELF magnetic fields. *Intl Arch Occup Environ Health* 62(4):289-293 (1990).
- Kaczmarek LK, Adey WR. The efflux of  $^{45}\text{Ca}^{2+}$  and (3H)gamma-aminobutyric acid from cats cerebral cortex. *Brain Res* 63:331-42 (1973).
- Karasek, M., Woldanska-Okonska, M., Czernicki, J., Zylinska, K. and Swietoslowski, J., 1998: "Chronic exposure to 2.9 mT, 40 Hz magnetic field reduces melatonin concentrations in humans". *J Pineal Research* 25(4): 240-244.
- Kellenyi, L, Thuroczy, G, Faludy, B, Lenard, L, 1999: Effects of mobile GSM radiotelephone exposure on the auditory brainstem response (ABR). *Neurobiology* 7:79-81.
- Kheifets LI, Afifi AA, Buffler, Zhang ZW. Occupational electric and magnetic field exposure and brain cancer: a meta-analysis. *J Occup Environ Med* 37(12):1327-1341 (1995).
- Kheifets LI, Gilbert ES, Sussman SS, Guenel P, Sahl JD, Savitz DA, Theriault G. Comparative analyses of the studies of magnetic fields and cancer in electric utility workers: studies from France, Canada and the United States. *Occup Environ Med* 56(8):567-574 (1999).
- Khudnitskii, SS, Moshkarev, EA, Fomenko, TV, 1999: [On the evaluation of the influence of cellular phones on their users]. [Article in Russian] *Med Tr Prom Ekol* (9):20-24.
- Koivisto, M, Revonsuo, A, Krause, C, Haarala, C, Sillanmaki, L, Laine, M, Hamalainen, H, 2000: Effects of 902 MHz electromagnetic field emitted by cellular telephones on response times in humans. *Neuroreport* 11(2):413-415.
- Kolomytkin O, Kuznetsov V, Yurinska M, Zharikova A, Zharikov S. Response of brain receptor systems to microwave energy exposure. In *On the nature of electromagnetic field interactions with biological systems* (Allan H Frey ed) 1994; 195-206.
- König HL, Behavioural changes in human subjects associated with ELF electric fields. In: *ELF and VLF electromagnetic field effects* (Persinger MA ed), New York, Plenum Press, 1974; 81-99.
- Kraut A, Tate R, Tran NM. Residential electric consumption and childhood cancer in Canada (1971-1986). *Arch Environ Health* 49(3):156-159 (1994).
- Kwee, S, Raskmark, P, 1997: Radiofrequency electromagnetic fields and cell proliferation. Presented at the Second World Congress for Electricity and Magnetism in Biology and Medicine, Bologna, Italy, June.
- Levallois, P., Dumont, M., Touitou, Y., Gingras, S., Masse, B., Gauvinm, D., Kroger, E., Bourdages, M. and Douville, P., 2002: "Effects of electric and magnetic fields from high-power lines on female urinary excretion of 6-sulfatoxymelatonin". *Am J Epidemiol.* 154(7): 601-609.
- Lilienfeld AM, Tonascia J, Tonascia S, Libauer CA, Cauthen GM, Foreign Service health status study - evaluation of health status of foreign service and other employees from selected eastern European posts. Final Report (Contract number 6025-619073) to the U.S. Department of State, July 31, 1978, 429pp.
- Lin RS, Dischinger PC, Conde J, Farrel KP. Report on the relationship between the incidence of brain tumors and occupational electromagnetic exposure. *J Occup Med* 27:413-419 (1985).

- Loomis DP, Savitz DA. Mortality from brain cancer and leukaemia among electrical workers. *Br J Ind Med* 47(9):633-638 (1990).
- Löscher, W. and Käs, G., 1998: "Conspicuous behavioural abnormalities in a dairy cow herd near a TV and radio transmitting antenna". *Prakt. Tierarzt* 79(5): 437-444 [In German]. [Practical Veterinary Surgeon 79(5): 437-444.]
- Mack W, Preston-Martin S, Peters JM. Astrocytoma risk related to job exposure to electric and magnetic fields. *Bioelectromagnetics* 12(1):57-66 (1991).
- Maes A, Collier M, Van Gorp U, Vandoninck S, Verschaeve L, 1997: Cytogenetic effects of 935.2-MHz (GSM) microwaves alone and in combination with mitomycin C. *Mutat Res* 393(1-2): 151-156.
- Mallin K, Rubin M, Joo E. Occupational cancer mortality in Illinois white and black males, 1979-1984, for seven cancer sites. *Am. J. Ind. Med* 15(6): 699-717 (1989).
- Mann K, Roschke J. Effects of pulsed high-frequency electromagnetic fields on human sleep. *Neuropsychobiology* 33: 41-47 (1996).
- Matanoski GM, Elliot EA, Breyse PN, Lynberg MC. Leukemia in telephone linemen. *Am J Epidemiol* 137(6):609-619 (1993).
- Mattos IE, Koifman S. Cancer mortality among electricity utility workers in the state of Sao Paulo, Brazil. *Rev Saude Publica* 30(6):564-575 (1996).
- Meinert R, Michaelis J. Meta-Analysis of studies on the association between electromagnetic fields and childhood cancer. *Radiat Environ Biophys* 35(1):11-18 (1996).
- Meltz ML. Biological effects versus health effects: an investigation of the genotoxicity of microwave radiation. In: *Radiofrequency Radiation Standards*, NATO ASI Series (B.J. Klaueberg Ed). New York, Plenum Press, 1995: 235-241.
- Mild H.K., Oftedak G, Sandstrom M, Wilen J, Tynes T, Haugsdal B, Hauger E. Comparison of symptoms experienced by users of analogue and digital mobile phones - a Swedish-Norwegian epidemiological study Rpt No 1998:23. National Institute for Working Life, Umea, Sweden (1998).
- Milham S Jr. Increased incidence of cancer in a cohort of office workers exposed to strong magnetic fields. *Am J Ind Med* 30(5):702-704 (1996).
- Milham S. Mortality in workers exposed to electromagnetic fields. *Environ Health Perspectives* 62:297-300(1985).
- Milham S. Increased mortality in amateur radio operators due to lymphatic and hematopoietic malignancies. *Am J Epidemiol* 127(1):50-54 (1988).
- Miller, RD, Neuberger JS, Gerald KB. *Epidemiologic Reviews* 19(2):273-293.
- Miller AB, To T, Agnew DA, Wall C, Green LM. Leukemia following occupational exposure to 60-Hz electric and magnetic fields among Ontario electric utility workers. *Am J Epidemiol* 144(2):150-160(1996).
- Moscovici B, Lavyel A, Ben-Itzhac D. Exposure to electromagnetic radiation among workers. *Fam Physician* 3(3):121 (1974).

- Motluk, A., 1997: "Radio head: The brain has its own FM receiver". *New Scientist*, 25 October 1997, p17.
- Nicholas JS, Lackland DT, Butler GC, Mohr LC Jr, Dunbar JB, Kraune WT, Grosche B, Hoel DG. Cosmic radiation and magnetic field exposure to airline flight crews. *Am J Ind Med* 34(6):574-580 (1998).
- Nicholas JS, Lackland DT, Dosemeci M, Mohr LC Jr, Dunbar JB, Grosche B, Hoel DG. Mortality among US commercial pilots and navigators. *J Occup Environ Med* 40(11):980-985 (1998).
- Olsen JH, Jensen JK, Nielsen A, Schulgen G. Electromagnetic fields from high-voltage transmissions and cancer in childhood. *Ugeskr Laeger* 156(17):2579-2584 (1994).
- Olsen JH, Nielson A, Schulgen G. Residence near high voltage facilities and risk of cancer in children. *BMJ* 307:891-895 (1993).
- Pahl, H.L., 1999: "Signal transduction from the endoplasmic reticulum to the cell nucleus". *Physiological Reviews*, 79(3): 683-701.
- Park RM, Silverstein MA, Green MA, Mirer FE. Brain cancer mortality at a manufacture of aerospace electrochemical systems. *Am J Ind Med* 17(5):537-552 (1990).
- Pearce N, Reif J, Fraser J. Case-control studies of cancer in New Zealand electrical workers. *Int J Epidemiol* 18(1): 55-59 (1989).
- Perry FS, Reichmanis M, Marino A, Becker RO. Environmental power-frequency magnetic fields and suicide. *Health Phys* 41(2):267-277 (1981).
- Pfluger, D.M. and Minder, C.E., 1996: "Effects of 16.7 Hz magnetic fields on urinary 6-hydroxymelatonin sulfate excretion of Swiss railway workers". *J Pineal Research* 21(2): 91-100.
- Phillips, J.L., Ivaschuk, O., Ishida-Jones, T., Jones, R.A., Campbell-Beachler, M. and Haggren, W., 1998: "DNA damage in molt-4 T-lymphoblastoid cells exposed to cellular telephone radiofrequency fields in vitro". *Bioelectrochem Bioenerg* 45: 103-110.
- Polk C, 1982: "Schumann Resonances". In: *CRC Handbook of Atmospherics*, 2 (Hans Volland ed). Boca Raton, Florida: CRC Press, 111-177.
- Pollack, H., 1979: "Epidemiologic data on American personnel in the Moscow Embassy", *Bull. N.Y. Acad. Med*, 55(11): 1182-1186.
- Pollack H. The Microwave Syndrome. *Bull NY Acad Med* 55: 1240-1243 (1979).
- Preece AW, Iwi G, Davies-Smith A, Wesnes K, Butler S, Lim E, Varey A., Effect of a 915-MHz simulated mobile phone signal on cognitive function in man. *Int J Radiat Biol* 75(4): 447-456 (1999).
- Preston-Martin S, Navidi W, Thomas D, Lee PJ, Bowman J, Pogoda J. Los Angeles study of residential magnetic fields and childhood brain tumors. *Am J Epidemiol* 143:105-119 (1996).
- Preston-Martin S, Lewis S, Winkelmann R, Borman B, Auld J, Pearce N. Descriptive epidemiology of primary cancer of the brain, cranial nerves, and cranial meninges in New Zealand, 1948-88. *Cancer Causes and Control* 4(6):529-538 (1993).



- Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males Los Angeles County. *Cancer Research* 49:6137 (1989).
- Reiter, R.J., and Robinson, J. Melatonin: your body's natural wonder drug. New York: Bantam Books, 1995.
- Reiter RJ. Melatonin biosynthesis, regulation and effects. In: The Melatonin Hypothesis: breast cancer and electric power (Richard Stevens, Barry Wilson and Larry Anderson eds). Richland, Battelle Press, 1997; 25-48.
- Reiter, R.J., 1994: "Melatonin suppression by static and extremely low frequency electromagnetic fields: relationship to the reported increased incidence of cancer". *Reviews on Environmental Health*. 10(3-4): 171-86, 1994.
- Reiter, R.J. and Robinson, J, 1995: "Melatonin: Your body's natural wonder drug". Publ. Bantam Books, New York.
- Repacholi MH, Basten A, Gebiski V, Noonan D, Finnie JH, Harris AW. Lymphomas in E $\mu$ -*Pim1* Transgenic Mice Exposed to Pulsed 900 MHz Electromagnetic Fields. *Radiation Research* 147:631-640 (1997).
- Robinette CD, Silverman C, Jablon S. Effects upon health of occupational exposure to microwave radiation (radar). *Am J Epidemiol* 112(1):39-53 (1980).
- Rodvall Y, Ahlbom A, Stenlund C, Preston-Martin S, Lindh T, Spannare B. Occupational exposure to magnetic fields and brain tumors in central Sweden. *Eur J Epidemiol* 14(6):563-569 (1998).
- Rosen, L.A., Barber, I. and Lyle D.B., 1998: "A 0.5 G, 60 HZ magnetic field suppresses melatonin production in pinealocytes". *Bioelectromagnetics* 19: 123-127.
- Rothman KJ, Loughlin JE, Funch DP, Dreyer NA. Overall mortality of cellular telephone customers. *Epidemiology* 7(3): 303-305 (1996).
- Salford, L.G., Brun, A., Stureson, K., Eberhardt, J.L. and Persson, B.R.R., 1994: Permeability of the Blood-Brain Barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50 and 200 Hz.
- Salisbury DA, Band PR, Threlfall WJ, Gallagher RP. Mortality among British Colombia pilots. *Aviat Space Environ Med* 62(4):351-352 (1991).
- Santana VS, Silva M, Loomis D. Brain neoplasms among naval military men. *Int J Occup Environ Health* 5(2):88-94(1999).
- Savitz DA, Loomis DP Magnetic field exposure in relation to leukemia and brain cancer mortality among electric utility workers. *Am J Epidemiol* 141(2):123-34 1995.
- Savitz DA, Kaune WT. Childhood cancer in relation to a modified residential wire code. *Environ Health Perspect* 101(1): 76-80 (1993).
- Savitz DA, John EM, Kleckner RC. Magnetic field exposure from electric appliances and childhood cancer. *Am J Epidemiol* 131(5):763-773 (1990).
- Savitz DA, Wachtel H, Barnes FA, John EM, Tvrdik JG Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *Am J Epidemiol* 128(1):21-38 (1988)

- Savitz DA, Checkoway H, Loomis DP. Magnetic field exposure and neurodegenerative disease mortality among electric utility workers. *Epidemiology* 9(4):398-404 (1998).
- Savitz DA, Loomis DP, Tse CK. Electrical occupations and neurodegenerative disease: analysis of U.S. mortality data. *Arch Environ Health* 53(1):71-74 (1998).
- Schirmacher, A, Bahr, A, Kullnick, U, Stoegbauer, F, 1999: Electromagnetic fields (1.75 GHz) influence the permeability of the blood-brain barrier in cell culture model. Presented at the Twentieth Annual Meeting of the Bioelectromagnetics Society, St. Pete Beach, FL, June.
- Schlehofer B, Kunze S, Sachsenheimer W, Blettner M, Niehoff D, Wahrendorf J. Occupational risk factors for brain tumors: results from a population-based case-control study in Germany. *Cancer Causes and Control* 1(3):209-215 (1990).
- Schreiber GH, Swaen GM, Meijers JM, Slangen JJ, Sturmans F. Cancer mortality and residence near electricity transmission equipment: a retrospective cohort study. *Int J Epidemiol* 22(1):9-15 (1993).
- Schwan HP, Foster KR. RF-field interactions with biological systems: electrical properties and biophysical mechanisms. *Proc IEEE* 68(1): 104-113 (1980).
- Schwartz JL, House DE, Mealing AR. Exposure of frog hearts to CW or amplitude modulated VHF fields: selective efflux of calcium ions at 16 Hz. *Bioelectromagnetics* 11: 349-358 (1990).
- Selvin S, Schulman J, Merrill DW. Distance and risk measurements for the analysis of spatial data: a case study of childhood cancers. *Soc Sc. Med* 34(7):769-777 (1992).
- Shandala MG, Dumanski UD, Rudnev MI, Ershova LK, Los IP. Study of nonionizing microwave radiation effects on the central nervous system and behavior reactions. *Environ Health Perspect* 30:115-121 (1979)
- Sobel E, Davanipour DVM. Electromagnetic field exposure may cause increased production of amyloid beta and eventually lead to Alzheimer's disease. *Neurology* 47(12):1594-1600 (1996).
- Sobel E, Davanipour Z, Sulkava R, Erkinjuntti T, Wikstrom J, Henderson VW, Bucjwalter G, Bowman D, Lee P-J. Occupations with exposure to electromagnetic fields: a possible risk factor for Alzheimer's Disease. *Am J Epidemiol* 142(5): 515-524 (1995).
- Sobel E, Dunn M, Davanipour DVM, Qian MS, Chui MD. Elevated risk of Alzheimer's disease among workers with likely electromagnetic field exposure. *Neurology* 47(12): 1477-1481 (1996).
- Speers MA, Dobbins JG, Miller VS. Occupational exposures and brain cancer mortality: a preliminary study of East Texas Residents. *Am J Ind Med* 13:629-638 (1988).
- Stark, K.D.C., Krebs, T., Altpeter, E., Manz, B., Griol, C. and Abelin, T., 1997: "Absence of chronic effect of exposure to short-wave radio broadcast signal on salivary melatonin concentrations in dairy cattle". *J Pineal Research* 22: 171-176.
- Strickland, D., Smith, S.A., Dolliff, G., Goldman, L. and Roelofs, R.I., 1996: "Amyotrophic lateral sclerosis and occupational history. A pilot case-control study". *Arch Neurol* 53(8): 730-733.
- Szmigielski S, Bielec M, Lipski S, Sokolska G. Immunological and cancer-related aspects of exposure to low level microwave and radiofrequency fields. In: *Modern Bioelectricity* (Marino A ed). New York, Marcel Bekker, 1988:861-925.

- Szmigielski S. Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation. *Sci Total Env* 180:9-17 (1996).
- Theriault G, Goldberg M, Miller AB, Armstrong B, Guenel P, Deadman J, Imbernon E, To T, Chevalier A, Cyr D, et.al. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970-1989. *Am J Epidemiol* 139(6): 550-572 (1994).
- Theriault G. Electromagnetic fields and cancer risks. *Rev Epidemiol Sante Publique* 40(Suppl 1):S55-62 (1992).
- Thomas TL, Stolley PD, Stemhagen A, Fontham ETH, Bleecker ML, Stewart PA, Hoover RN. Brain tumor mortality risk among men with electrical and electronic jobs: A case-control study. *J Natl Cancer Inst* 79(2):233-238 (1987).
- Tice R, Hook G, McRee DI. Chromosome aberrations from exposure to cell phone radiation. *Microwave News*, Jul/Aug (1999) p7
- Tomenius L. 50-Hz electromagnetic environment and the incidence of childhood tumors in Stockholm County. *Bioelectromagnetics* 7(2):191-207 (1986).
- Tornqvist S, Norell S, Ahlbom A, Knave B. Cancer in the electric power industry. *Br J Ind Med* 43(3):212-213 (1986).
- Tornqvist S, Knave B, Ahlbom A, Persson T. Incidence of leukaemia and brain tumours in some 'electrical occupations. *Br J Ind Med* 48: 597-603 (1991).
- Tynes T, Haldorsen T. Electromagnetic fields and cancer in children residing near Norwegian high-voltage power lines. *Am J Epidemiol* 145(3):219-226(1997).
- Tynes T, Anderson A, Langmark F. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. *Am J Epidemiol* 136(1):81-88 (1992).
- Vaneeck, J., 1998: "Cellular Mechanisms of Melatonin Action". *Physiol. Rev.* 78: 687-721.
- Velizarov, S, Raskmark, P, Kwee, S, 1999: The effects of radiofrequency fields on cell proliferation are non-thermal. *Bioelectrochem Bioenerg* 48(1):177-180.
- Verkasalo PK, Haprio J, Varjonen J, Romanov K, Heikkila K, Koskenvuo M. Magnetic fields of transmission lines and depression. *Am J Epidemiol* 146(12):1037-1045 (1997).
- Verkasalo PK, Pukkala E, Hongisto MY, Valjus JE, Jarvinen PJ, Heikkila, KV, Koskenvuo M. Risk of cancer in Finnish children living close to power lines. *BMJ* 307(6909):895-899 (1993).
- Verschaeve, L., Slaets, D., Van Gorp, U., Maes, A. and Vanderkom, J., 1994: "In vitro and in vivo genetic effects of microwaves from mobile phone frequencies in human and rat peripheral blood lymphocytes". *Proceedings of Cost 244 Meetings on Mobile Communication and Extremely Low Frequency field: Instrumentation and measurements in Bioelectromagnetics Research*. Ed. D, Simunic, pp 74-83.
- Vignati M, Giuliani L. Radiofrequency exposure near high-voltage lines. *Environ Health Perspect* 105 (Suppl 6): 1569-1573 (1997).

- Vijayalaxmi BZ, Frei MR, Dusch SJ, Guel V, Meltz ML, Jauchem JR. Frequency of micronuclei in the peripheral blood and bone marrow of cancer-prone mice chronically exposed to 2450 MHz radiofrequency radiation. *Radiat Res* 147: 495-500 (1997).
- Von Klitzing L. Low frequency pulsed electromagnetic fields influence EEG of man. *Physica Medica* 11(2): 77-80 (1995).
- Wang SG. 5-HT contents change in peripheral blood of workers exposed to microwave and high frequency radiation. *Chung Hua Yu Fang I Hsueh Tsa Chih* 23(4): 207-210 (1989).
- Wang, S.G. 1989: "5-HT contents change in peripheral blood of workers exposed to microwave and high frequency radiation". *Chung Hua Yu Fang I Hsueh Tsa Chih* 23(4): 207-210.
- Washburn EP, Orza MJ, Berlin JA, Nicholson WJ, Todd AC, Frumkin H, Chalmers TC. Residential proximity to electric transmission and distribution equipment and risk of childhood leukaemia, childhood lymphoma and childhood nervous system tumors: systematic review, evaluation and meta-analysis. *Cancer Causes and Control* 5(4):299-309 (1994).
- Wertheimer, N, Leeper E. Electrical wiring configurations and childhood cancer. *Am J Epidemiol* 109(3):272-284 (1979)
- Wilson, B.W., Wright, C.W., Morris, J.E., Buschbom, R.L., Brown, D.P., Miller, D.L., Sommers-Flannigan, R. and Anderson, L.E., 1990: "Evidence of an effect of ELF electromagnetic fields on human pineal gland function". *J Pineal Research* 9(4): 259-269.
- Wood, A.W., Armstrong, S.M., Sait, M.L., Devine, L. and Martin, M.J., 1998: "Changes in human plasma melatonin profiles in response to 50 Hz magnetic field exposure". *J Pineal Research* 25(2): 116-127.
- Wever R, ELF-effects on Human Circadian Rhythms. In: *ELF and VLF Electromagnetic Field Effects*, (Persinger MA ed). New York, Plenum Press; 1974; 101-144.
- Wilson BW, Wright CW, Morris JE, Buschbom RL, Brown DP, Miller DL, Sommers-Flannigan R, Anderson LE. 1990: Evidence of an effect of ELF electromagnetic fields on human pineal gland function. *J Pineal Research* 9(4): 259-269 (1990).
- Wood AW, Armstrong SM, Sait ML, Devine L, Martin MJ. Changes in human plasma melatonin profiles in response to 50 Hz magnetic field exposure. *J Pineal Research* 25(2): 116-127 (1998).
- Yaga, K, Reiter, R.J., Manchester, L.C., Nieves, H., Sun, J.H. and Chen, L.D., 1993: "Pineal sensitivity to pulsed magnetic fields changes during the photoperiod. *Brain Res Bulletin*, 30 (1-2): 153-156.
- Youbicier-Simo, BJ, Lebecq, JC, Bastide, M, 1998: Mortality of chicken embryos exposed to EMFs from mobile phones. Presented at the Twentieth Annual Meeting of the Bioelectromagnetics Society, St. Pete Beach, FL, June.
- Zaret MM. Potential hazards of hertzian radiation and tumors. *NY State J Med* 146-147 (1977).

Neurological; The effects of mobile-phone electromagnetic fields on brain electrical activity: a critical analysis of the literature. Electromagn Biol Med. (Marino et al) (Abstract); 2009

Display Settings:  
Abstract  
Send to:

Electromagn Biol Med. 2009;28(3):250-74. doi: 10.3109/15368370902918912.

## The effects of mobile-phone electromagnetic fields on brain electrical activity: a critical analysis of the literature.

Marino AA, Carrubba S.

### Source

Department of Orthopaedic Surgery, LSU Health Sciences Center, Shreveport, LA 71130-3932, USA. amarino@lsuhsc.edu

### Abstract

We analyzed the reports in which human brain electrical activity was compared between the presence and absence of radio-frequency and low-frequency electromagnetic fields (EMFs) from mobile phones, or between pre- and post-exposure to the EMFs. Of 55 reports, 37 claimed and 18 denied an EMF-induced effect on either the baseline electro encephalogram (EEG), or on cognitive processing of visual or auditory stimuli as reflected in changes in event-related potentials. The positive reports did not adequately consider the family-wise error rate, the presence of spike artifacts in the EEG, or the confounding role of the two different EMFs. The negative reports contained neither positive controls nor power analyses. Almost all reports were based on the incorrect assumption that the brain was in equilibrium with its surroundings. Overall, the doubt regarding the existence of reproducible mobile-phone EMFs on brain activity created by the reports appeared to legitimate the knowledge claims of the mobile-phone industry. However, it funded, partly or wholly, at least 87% of the reports. From an analysis of their cognitive framework, the common use of disclaimers, the absence of information concerning conflicts of interest, and the industry's donations to the principal EMF journal, we inferred that the doubt was manufactured by the industry. The crucial scientific question of the pathophysiology of mobile-phone EMFs as reflected in measurements of brain electrical activity remains unanswered, and essentially unaddressed.

PMID:

20001702

[PubMed - indexed for MEDLINE]

[Publication Types, MeSH Terms](#)

Publication Types

Meta-Analysis

Research Support, Non-U.S. Gov't

MeSH Terms

Brain/physiology\*

Brain/radiation effects\*

Cellular Phone\*

Electric Conductivity\*

Electromagnetic Fields/adverse effects\*

Environmental Exposure/adverse effects

Humans

Radio Waves/adverse effects

[LinkOut - more resources](#)

Full Text Sources

Informa Healthcare

EBSCO

Other Literature Sources

COS Scholar Universe

Labome Researcher Resource - ExactAntigen/Labome

Medical

Electromagnetic Fields - MedlinePlus Health Information



Autism and EMF? Plausibility of a pathophysiological link.  
Pathophysiology, Part I. (Herbert et al); 2013





# Autism and EMF? Plausibility of a pathophysiological link – Part I

Martha R. Herbert<sup>a,\*</sup>, Cindy Sage<sup>b</sup>

<sup>a</sup> *TRANSCEND Research Program Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02129, USA*

<sup>b</sup> *Sage Associates, Santa Barbara, CA, USA*

Received 10 February 2013; received in revised form 6 May 2013; accepted 15 July 2013

## Abstract

Although autism spectrum conditions (ASCs) are defined behaviorally, they also involve multileveled disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency exposures (EMF/RFR). Part I of this paper will review the critical contributions pathophysiology may make to the etiology, pathogenesis and ongoing generation of core features of ASCs. We will review pathophysiological damage to core cellular processes that are associated both with ASCs and with biological effects of EMF/RFR exposures that contribute to chronically disrupted homeostasis. Many studies of people with ASCs have identified oxidative stress and evidence of free radical damage, cellular stress proteins, and deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASCs may be due to genetics or may be downstream of inflammation or environmental exposures. Cell membrane lipids may be peroxidized, mitochondria may be dysfunctional, and various kinds of immune system disturbances are common. Brain oxidative stress and inflammation as well as measures consistent with blood–brain barrier and brain perfusion compromise have been documented. Part II of this paper will review how behaviors in ASCs may emerge from alterations of electrophysiological oscillatory synchronization, how EMF/RFR could contribute to these by de-tuning the organism, and policy implications of these vulnerabilities. Changes in brain and autonomic nervous system electrophysiological function and sensory processing predominate, seizures are common, and sleep disruption is close to universal. All of these phenomena also occur with EMF/RFR exposure that can add to system overload ('allostatic load') in ASCs by increasing risk, and worsening challenging biological problems and symptoms; conversely, reducing exposure might ameliorate symptoms of ASCs by reducing obstruction of physiological repair. Various vital but vulnerable mechanisms such as calcium channels may be disrupted by environmental agents, various genes associated with autism or the interaction of both. With dramatic increases in reported ASCs that are coincident in time with the deployment of wireless technologies, we need aggressive investigation of potential ASC – EMF/RFR links. The evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels now known to be biologically disruptive, and strong, interim precautionary practices are advocated.

© 2013 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Autism; EMF/RFR; Cellular stress; Oxidative stress; Mitochondrial dysfunction; Oscillatory synchronization; Environment; Radiofrequency; Wireless; Children; Fetus

## 1. Introduction

The premise of this review is that although scant attention has been paid to possible links between electromagnetic fields and radiofrequency radiation exposures (EMF/RFR) and Autism Spectrum Conditions (ASCs), such links probably exist. The rationale for this premise is that the physiological impacts of EMF/RFR and a host of increasingly well-documented pathophysiological phenomena in ASCs have remarkable similarities, spanning from cellular and

oxidative stress to malfunctioning membranes, channels and barriers to genotoxicity, mitochondrial dysfunction, immune abnormalities, inflammatory issues, neuropathological disruption and electrophysiological dysregulation – in short, multi-scale contributors to de-tuning the organism. Additional support may be found in the parallels between the rise in reported cases of ASCs and the remarkable increases in EMF/RFR exposures over the past few decades

Reviewing these similarities does not prove that these parallels imply causality. Moreover, the physiological processes affected by EMF/RFR are also impacted by other environmental factors, and are known to be present in myriad other chronic illnesses. A set of in-depth reviews on the

\* Corresponding author.

E-mail address: [drmarthaherbert@gmail.com](mailto:drmarthaherbert@gmail.com) (M.R. Herbert).

science and public health policy implications of EMF/RFR has been published in a special issue of Pathophysiology 16 (2,3) 2009. This two-volume special issue of Pathophysiology offers a broad perspective on the nature of health impacts of man-made EMFs, documenting biological effects and health impacts of EMFs including genotoxicity, neurotoxicity, reproductive and developmental effects, physiological stress, blood–brain barrier effects, immune system effects, various cancers including breast cancer, glioma and acoustic neuroma, Alzheimer's disease; and the science as a guide to public health policy implications for EMF diseases [1]. Many of these reviews have been updated in the BioInitiative 2012 Report [2], with 1800 new papers added. Further reinforcement is published in seminal research reviews including the two-volume Non-Thermal effects and Mechanisms of Interaction between Electromagnetic Fields and Living Matter, Giuliani L and Soffritti, M (Eds.), ICEMS, Ramazzini Institute, Bologna, Italy (2010) [3]; the World Health Organization INTERPHONE Final Report (2010) [4]; and the WHO International Agency for Research on Cancer RFR Monograph [5] designating RFR as a Group 2B Possible Human Carcinogen. The National Academy of Sciences Committee on Identification of Research Needs Relating to Potential Biological or Adverse Health Effects of Wireless Communication Devices (2008) [6] called for health research on wireless effects on children and adolescents and pregnant women; wireless personal computers and base station antennas; multiple element base station antennas under highest radiated power conditions; hand-held cell phones; and better dosimetric absorbed power calculations using realistic anatomic models for both men, women and children of different height and ages. Yet EMF/RFR does not need to be a unique contributor to ASCs to add significantly to system overload ('allostatic load') and dysfunction [7]. Even so these pathophysiological overlaps do suggest that the potential for an EMF/RFR-ASC connection should be taken seriously, and that their biological fragility may make many with ASCs more likely to experience adverse EMF/RFR impacts. This is a sufficient basis to recommend that precautionary measures should be implemented, that further research should be prioritized, and that policy level interventions based on existing and emerging data should be designed and pursued. Moreover, pursuing this link could help us understand ASCs better and find more ways to improve the lives of people with ASCs and of so many others.

This paper is divided into two parts. Part I (<http://dx.doi.org/10.1016/j.pathophys.2013.08.001>) describes the pathophysiology and dynamism of common behavioral manifestations in autism, and pathophysiological damage to core cellular processes that is associated both with ASCs and with impacts of EMF/RFR. Part II (<http://dx.doi.org/10.1016/j.pathophys.2013.08.002>) reviews how behaviors in ASCs may emerge from alterations of electrophysiological oscillatory synchronization and how EMF/RFR could contribute to these by de-tuning the organism. Part II also discusses public health implications,

and proposes recommendations for harm prevention and health promotion.

## 2. Physiological pathogenesis and mechanisms of autism spectrum conditions

### 2.1. How are biology and behavior related?

Appreciating the plausibility of a link between ASCs and EMF/RFR requires considering the relationship between ASC's behavioral and biological features. ASCs were first labeled as 'autism' in 1943 by Leo Kanner, a child psychiatrist who extracted several key behavioral features, related to communication and social interaction challenges and a tendency toward restricted interests and repetitive behaviors [8]. There has been some modification of the characterization of these behavioral features, but ASCs are still defined behaviorally, although sensory issues such as hypo- or hyper-reactivity have recently been included in the diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders or DSM-V) [9,10].

#### 2.1.1. Transduction is fundamental but poorly understood

To evaluate how an environmental factor such as EMF/RFR could lead to autism and/or influence its severity or incidence, we examine how effects of EMF/RFR exposure may be transduced into changes in nervous system electrical activity, and how these in turn generate the set of behaviors we have categorized as 'autism.' [11] This means not taking behaviors as given, or as purely determined by genetics, but exploring the full range of biology that generates these features and challenges.

#### 2.1.2. More than brain

Although 'autism' has long been considered to be a psychiatric or neurological brain-based disorder [12,13], people diagnosed with ASCs often have many biological features including systemic pathophysiological disturbances (such as oxidative stress, mitochondrial dysfunction and metabolic and immune abnormalities) [14–17] as well as symptomatic medical comorbidities (such as gastrointestinal distress, recurrent infections, epilepsy, autonomic dysregulation and sleep disruption) [18–26] in addition to the core defining behaviors [27]. Because of variability among individuals, the relevance of many of these biological features has been dismissed as secondary and not intrinsically related to the 'autism.'

#### 2.1.3. Heterogeneity: more genetic and environmental than physiological

Presently large numbers of genes and environmental contributors to ASCs are under consideration. Over 800 genes have been associated with ASCs, and over 100 different rare genetic syndromes are frequently accompanied by ASCs, but

no clear unifying mechanism has been identified [28–33]. Similarly, a large number of potential environmental contributors are under investigation ranging from toxicants and Vitamin D deficiency or failure to take prenatal vitamins to air pollution and stress or infection in pregnancy [34–41].

By contrast, a smaller set of disturbances are showing up physiologically as common across substantial numbers of people with ASCs – as well as in myriad other chronic conditions whose prevalence also appears to be increasing [42,43]. These include oxidative stress, inflammation, and mitochondrial dysfunction. EMF/RFR exposure is associated with many of the same biological effects and chronic health conditions [1]. This environmentally vulnerable physiology [44], which may serve as final common pathways triggered by diverse genetic and environmental contributors, will be discussed in Section 3 of Part I as well as in Part II; it may or may not need to rest on underlying genetic vulnerability.

#### 2.1.4. EMF/RFR research may help us understand how ASCs ‘work’

Some correlations between biological and behavioral features have been identified – e.g., a higher level of immune abnormalities correlates with more aberrant behaviors [26,45–50]. In order to move beyond correlations to identifying *mechanisms* by which the *transduction of pathophysiology into behavior* might actually occur, an important component is studying the relationship between systemic pathophysiology and nervous system electrophysiology.

The brain is simultaneously a tissue-based physical organ that can be compromised by cellular pathophysiology as well as altered developmental processes and an information processing system that operates through networks of synchronized electrical oscillations (brain waves) – and EMF/RFR impacts may occur directly at both of these levels. To date the emphasis in ASC research has largely been on ‘structure-function’ relationships that have been anatomy-centered. Thus, exploring how EMF/RFR impacts ASCs may answer questions of how pathophysiological and electrophysiological information-processing interacts.

### 2.2. Time courses of mechanisms

Researchers have mainly looked for causes of autism in mechanisms that occur early and create permanent change or damage. This approach is logical if one assumes that genetic influences are overwhelmingly predominant, and ‘autism’ is a fixed lifelong trait. However evidence is emerging that ASCs may be more state-like and variable than trait-like and fixed.

#### 2.2.1. Plasticity

A remarkable shift is occurring in conceptual thinking about ASCs and brain plasticity [51]. There are growing numbers of reports of improvement and loss of diagnosis, reversal of neurological symptoms in a growing number of mouse models of genetic syndromes that in humans prominently feature autism [52–62], short-term pharmaceutically-induced

improvement in brain connectivity [63], and transient reversal or abeyance of symptomatology under various circumstances (including fever, fluid-only diet, and certain antibiotic treatments [50,64]). Reversals undermine the idea that ASCs derive from an intrinsically ‘broken brain’, and short time frames of marked improvement cannot be accounted for by remodeling of the brain’s anatomical substrate [65]. ‘Brain waves’ and their synchronization, on the other hand, could easily vary over short time periods.

Also, evidence of average to superior intelligence in most people with autism [66,67], as well as of domains of perceptual superiority [68–76], call into question the assumption that ASCs are intrinsically associated with cognitive deficits.

#### 2.2.2. Mechanisms that operate actively throughout the life-course

EMF/RFR effects can occur within minutes (Blank, 2009) and may, in part, explain clinical reports of ‘intermittent autism’ – for example, some children with mitochondrial disease who have ups and downs of their bioenergetics status ‘have autism’ on their bad days but don’t display autistic features on their good days [77]. These children with their vulnerable, barely compensated mitochondria could very well be teetering right at the brink of a minimally adequate interface of metabolic and electrophysiological dysfunction. Everyday exposures to allergens, infection, pesticide on the school playground, as well as EMF/RFR interference with electrophysiology might reasonably contribute to the bad days. Stabilizing more optimal nervous system performance [78] including through environmental control of excessive EMF/RFR exposure could perhaps achieve more ‘good days’.

#### 2.2.3. Pathophysiology and allostatic load

The model of ‘allostatic load’ – the sum total of stressors and burdens [79] – may be central to understanding how the many risk factors interact to create autism – and to create a spectrum of levels of severity across so many of ASD’s associated features. This accumulation increases chronic stress, and a growing number of papers document indicators of chronic stress in individuals with ASCs (as will be discussed in Part II). The ‘allostatic load’ concept dovetails well with a model of progressive exacerbation of pathophysiological disturbances that occurs in the pathogenesis of many chronic diseases [43]. It is also critical to understand that many different environmental factors converge upon a much smaller number of environmentally vulnerable physiological mechanisms [44], so that large numbers of small exposures may have effects from small numbers of large exposures.

EMF/RFR exposures have demonstrated biological effects at just about every level at which biology and physiology have been shown to be disrupted in ASCs. Further EMF/RFR has been shown to potentiate the impact of various toxicants when both exposures occur together [80]; this may be additive or more than additive. This suggests that EMF/RFR may synergize with other contributors and make things worse. A cascade of exposures interacting with vulnerabilities in

an individual can potentially lead to a tipping point for that person, such as the phenomenon of autistic regression experienced by a substantial subset of people with ASCs.

Just a few decades ago, EMF/RFR exposures were not present in the environment at today's levels. Levels have increased several thousand-fold or more in the past two decades from wireless technology alone; with unplanned side effects from pulsed RFR that is a newly classified Group 2B possible human carcinogen [5]. Nearly six billion people globally own wireless phones. Many millions are exposed to wireless exposures from use of wireless devices and wireless antenna facilities [81]. For this as well as for physiological reasons, 'allostatic loading' as a viable concept for the study of ASCs should reasonably address EMF/RFR as one of the exposures of relevance to the overall stress load, since it is now a chronic and unremitting exposure in daily life at environmentally relevant levels shown to cause bioeffects from preconception and pregnancy through infancy, childhood and the whole life-course.

### 3. Parallels in pathophysiology

This section will review parallels in pathophysiology between ASCs and impacts of EMF/RFR. It will begin with a review of mechanisms of direct impact and damage at the level of molecules, cells, tissues and genes. It will then move on to consider how these levels of damage lead to degradation of the integrity of functional systems including mitochondrial bioenergetics, melatonin metabolism, immune function and nervous system physiology. The review of parallels concludes with electromagnetic signaling and synchronized oscillation from membranes to nervous system. It will discuss how the ensemble of pathophysiological disturbances, which are themselves final common pathways that can be caused or worsened by many stressors, combine to converge upon electrophysiology. This leads to the implication that 'aberrant' neural systems and somatic function and behaviors might be better understood as consequences or 'outputs' of disturbed underlying physiology to which EMF/RFR is a plausible contributor.

#### 3.1. Damage: means and domains

ASCs have been conceptualized as 'neurodevelopmental' which has focused attention on how genes and environment could alter brain development. This leads to the unstated presumption that virtually everything important about the brain in ASCs has to do with differences in the way it was formed, and that all "malfunction" derives from this "malformation." In genetics this has led to a hunt for neurodevelopmental genes. There is no question that environmental impacts can alter brain development, and impact brain function across the lifespan.

However the influence of the environment on neurodevelopmental conditions such as ASCs does not stop there.

Evidence is accumulating showing that increased expression of genes associated with physiological dysregulation, as well as *single-nucleotide polymorphisms* (SNPs) associated with these issues, may be if anything more prominent than alterations of 'neurodevelopmental' genes [82]. In a study of gene expression in ASCs, Down syndrome and Rett syndrome, these authors state, "*(O)ur results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns. A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders.*" Others have also found pathophysiology-related genes as figuring most prominently in alterations of gene expression in ASC [83–86]. SNPs associated with methylation abnormalities, impaired glutathione synthesis and mitochondrial dysfunction also have been identified as significant risk factors.

Genetics may create risk, but the actual nervous system and health consequences probably come from dysfunction at the physiological level. As mentioned, evidence for pathophysiological dysfunction in ASCs increasingly abounds. In particular, a growing body of evidence widely reported in both the EMF/RFR and ASC literature documents immune aberrations, low total and reduced glutathione levels, lower activity of the anti-oxidative stress system and mitochondrial dysfunction. These phenomena may be both genetically and environmentally modulated. As will be discussed further below, they are certainly pertinent to the neurodevelopment of the brain, which has been by far the dominant focus autism research, but it does not stop there as they can significantly modulate brain function in real time, as well as shape the function of the entire organism, including the autonomic system, the cardiovascular, endocrine, immune, gastrointestinal and reproductive systems and more. These systemic impacts may in turn feed back into the nervous system, modulating how it functions.

#### 3.1.1. Cellular stress

**3.1.1.1. Oxidative stress.** Autism (ASC) research indicates that oxidative stress may be a common attribute amongst many individuals with autism. In the past decade the literature on this has moved from a trickle to a flood. Studies document reduced antioxidant capacity, increased indicators of oxidative stress and free radical damage, alterations in nutritional status consistent with oxidative stress, altered lipid profiles, and pertinent changes not only in blood but also in brain tissue. Associations of ASCs with environmental exposures such as air pollution and pesticides are indirectly supportive as well, since such exposures are linked in other literature to oxidative stress [43,87–101].

Reactive oxygen species are produced as a normal consequence of mitochondrial oxidative metabolism as well as other reactions, but when their number exceeds the cell's antioxidant capacity a situation of oxidative stress develops. It



is certainly the case that oxidative stress can be a consequence of exposures to chemical toxicants, or of the interactive impacts of toxicants, nutritional insufficiencies and genetic vulnerabilities. This set of risk factors has received considerable attention for the potential roles each component and various possible combinations could play in causing or exacerbating autism.

Less often mentioned in the ASC pathophysiology literature is that it is also well established that EMF/RFR exposures can be associated with oxidative damage. Published scientific papers that demonstrate the depth of EMF and RFR evidence reporting oxidative damage in human and animal models are profiled by Lai and colleagues [102–104]. These cellular effects can occur at low-intensity, legal levels of exposure that are now ‘common environmental levels’ for pregnant women, the fetus, the infant, the very young child, and the growing child as well as for adults. Electromagnetic fields (EMF) can enhance free radical activity in cells [105,106] particularly via the Fenton reaction, and prolonging the exposure causes a larger increase, indicating a cumulative effect. The Fenton reaction is a catalytic process of iron to convert hydrogen peroxides, a product of oxidative respiration in the mitochondria, into hydroxyl free radical, which is a very potent and toxic free radical [103,104]. Free radicals damage and kill organelles and cells by damaging macromolecules, such as DNA, protein and membrane components.

Further indications of a link to oxidative stress are findings that EMF and RFR at very low intensities can modulate glutamate, glutathione and GABA, and affect mitochondrial metabolism. Alterations in all these substances and processes have been documented in ASCs [25,86,89,90,92,107–127]. On the EMF/RFR side, Campisi et al. (2010) report that increased glutamate levels from 900 MHz cell phone frequency radiation on primary rat neocortical astroglial cell cultures induced a significant increase in ROS levels and DNA fragmentation after only 20 min with pulsed RFR at non-thermal levels [128].

Fragopoulou et al. (2012) conducted proteomics analysis of proteins involved in brain regulation in mice as a consequence of prolonged exposure to EMF [129]. They identified altered expression of 143 proteins, ranging from as low as 0.003-fold downregulation up to 114-fold overexpression with affected proteins including neural function-related proteins including Glial Fibrillary Acidic Protein (GFAP), alpha-synuclein, Glia Maturation Factor beta (GMF), apolipoprotein E (apoE), heat shock proteins, and cytoskeletal proteins (i.e., neurofilaments and tropomodulin), as well as proteins of brain metabolism such as aspartate aminotransferase and glutamate dehydrogenase. The authors pointed out that oxidative stress was consistent with some of these changes.

Aberrations in glutathione metabolism and deficiencies in reserves of reduced glutathione are increasingly associated with ASCs, both systemically and in the brain. The parallel with EMF/RFR impacts here is strong, since glutathione reduction associated with EMF/RFR is reported in at least

twenty three relevant research studies in both human and animal studies since 1998, including the following citations [130–144]. It is increasingly appreciated that glutathione is a final common pathway, a critical piece of environmentally vulnerable physiology, as glutathione reserves are compromised by an enormous number of environmental stressors, so that the cumulative impact upon glutathione may be far greater than could be predicted by the magnitude of any specific exposure [145], which supports an ‘allostatic loading’ model.

Also of note are studies showing that the effects of EMF/RFR can be reduced by supplementation with antioxidants and radical scavengers. As an example, Vitamins E and C reduced adverse impacts on rat endometrium from 900 MHz EMR exposure [137]. Ginkgo biloba has also prevented mobile phone-induced increases in malondialdehyde and nitric oxide levels in brain tissue as well as decreases in brain superoxide dismutase and glutathione peroxidase activities and increases in brain xanthine oxidase and adenosine deaminase activities, and treated rats were spared the histopathological cell injury found in the untreated rats [146]. Substantial further literature on antioxidants and radical scavengers is reviewed in Belyaev’s contribution to the Bioinitiative 2012 Report [147].

### 3.1.1.2. Stress protein (heat shock protein) responses.

Another well-documented effect of exposure to low-intensity extremely low frequency and RFR is the creation of stress proteins (heat shock proteins) indicating that a cell is being placed under physiological stress [148–154]. Heat shock proteins are in a family of inducible proteins that are initiated when any increased need for protection from stray electrons occurs [155,156]. The HSP response is generally associated with heat shock, exposure to toxic chemicals and heavy metals, and other environmental insults. HSP is a signal of cells in distress. Plants, animals and bacteria all produce stress proteins to survive environmental stressors like high temperatures, lack of oxygen, heavy metal poisoning, and oxidative stress. It should also be noted that the generation of HSP stress proteins can have constructive medical applications, such as protection from reperfusion of the heart following ischemic injury [157]. Another concomitant impact of cellular stress can be protein misfolding, which has been documented in association with exposure to EMF/RFR [158,159].

Although a number of papers have demonstrated increases in HSPs in people with ASCs [160–164], it has been investigated far less often than oxidative stress. Part of the research needed to study possible influences of EMF/RFR on ASCs would be more careful study of HSPs in ASCs.

### 3.1.2. Membranes and channels

#### 3.1.2.1. Cell membranes and lipid peroxidation.

Cell and organelle membranes play roles in partitioning cells from the extracellular milieu as well as in sustaining boundaries and regulating flow of materials between cellular compartments needing different metabolic parameters for their activities.

They also play critical roles in maintaining electrical differences and the flow of electricity.

Adey (2002) summarized studies that report cell membranes as the site of initial field transductive coupling.

*“Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both ELF and microwave fields for many neurotransmitters [165], hormones [166,167], growth-regulating enzyme expression [168–171], and cancer-promoting chemicals [172,173]. In none of these studies does tissue heating appear involved causally in the responses.” [174]*

Membranes are well-known targets of oxidative stress. Membrane damage is a major route through which free radical damage proliferates through the cellular system. Lipid peroxidation of membranes most often affects polyunsaturated fatty acids such as EPA and DHA which are the most abundant and vulnerable lipids in the brain where the damage they sustain can have serious impacts – DHA is 40% of PUFAs (brain polyunsaturated fatty acids). Lipid peroxidation of membranes has been identified as an effect of EMF/RFR in multiple studies [175,176]. A variety of other mechanisms for membrane alteration related to EMF/RFR have been intimated in the literature. Physicochemical properties of membranes such as phase transition of phosphatidylcholine can be shifted by non-thermal effects of microwave radiation [177]. Membrane potential and currents may also be impacted by pulsed radiofrequency fields [178]. This has been observed graphically in altered cellular movement in *Paramecium caudatum*, with these cells becoming broader, with a broader-appearing cytopharynx, with their pulse vesicles having difficulty in expelling their content outside the cell, and with less efficient movement of cilia [179] which the authors suggested might be due to targeting of the cellular membrane. The impacts on this unicellular organism may help us imagine what the impact of EMF/RFR might be on cells with some structural similarities, such as columnar epithelial cells and ciliated cells in mucosal surfaces in the respiratory system, digestive tract, uterus and fallopian tubes and central spinal cord.

Indications of lipid peroxidation of membranes has been documented in ASCs, including malonaldehyde and isoprostanes, as well as alteration of membrane phospholipids and prostaglandins [98,100,115,162,180–184]. In one study the isoprostane levels showed a bimodal distribution with the majority of ASC subjects showing moderate increase but a smaller group showing dramatic increases [183]. Thromboxane, reflecting platelet activation, was also elevated in one study [98]. Given that this phenomenon has been identified in many people with ASCs, it is plausible that such individuals will likely be more vulnerable to having such cellular injuries caused, worsened or both by EMF/RFR exposures.

**3.1.2.2. Calcium channels.** EMF/RFR exposures have been shown to alter or disturb calcium signaling [185] through a variety of mechanisms, including membrane leakage [186],

alteration of calcium-binding proteins and GFAP reactivity [187,188], and altered ultrastructural distribution of calcium and calcium-activated ATPases after exposure [189]. Adey (2002) provided an overview of key studies on calcium efflux and the importance of calcium in cell signaling. *“Early studies described calcium efflux from brain tissue in response to ELF exposures [190,191], and to ELF-modulated RF fields [190–193]. Calcium efflux from isolated brain subcellular particles (synaptosomes) with dimensions under 1.0  $\mu\text{m}$  also exhibit an ELF modulation frequency-dependence in calcium efflux, responding to 16 Hz sinusoidal modulation, but not to 50 Hz modulation, nor to an unmodulated RF carrier [194]. In the same and different cell culture lines, the growth regulating and stress responsive enzyme ornithine decarboxylase (ODC) responds to ELF fields [170,195] and to ELF-modulated RF fields.” [168,170,171,196].*

Dutta et al. (1992) reported:

*“Radio-frequency electromagnetic radiation (RFR) at 915 and 147 MHz, when sinusoidally amplitude modulated (AM) at 16 Hz, has been shown to enhance release of calcium ions from neuroblastoma cells in culture. The dose-response relation is unusual, consisting of two power-density “windows” in which enhanced efflux occurs, separated by power-density regions in which no effect is observed. Thus RFR affects both calcium-ion release and AChE activity in nervous system-derived cells in culture in a common dose-dependent manner.” [197]*

Alterations in calcium signaling impacts are of central importance in ASC pathophysiology, and have been documented to occur with some EMF/RFR exposures. Calcium channels play an important role in regulating neuronal excitability. Disturbance during development may be contributory to the development of ASCs, and is often associated with vulnerability to seizures. Gene alterations associated with a number of voltage-gated calcium channels have been identified in ASCs [198–202]. However, based on an examination of patient laboratory and phenotype data it has been argued that aberrant calcium signaling could be downstream: Palmieri and Persico (2010) suggest that *“an abnormal neuroimmune response as a relevant player in elevating intracellular  $\text{Ca}^{2+}$  levels, deranging neurodevelopment, driving oxidative stress, and ultimately affecting synaptic function and neural connectivity especially in long-range neuronal pathways physiologically responsible for integrated information processing” [203].* Peng and Jou (2010) have in turn shown how increased intracellular calcium can cause oxidative stress, and a vicious circle: *“... mitochondrial ROS [reactive oxygen species] rise can modulate  $\text{Ca}^{2+}$  dynamics and augment  $\text{Ca}^{2+}$  surge. The reciprocal interactions between  $\text{Ca}^{2+}$  induced ROS increase and ROS modulated  $\text{Ca}^{2+}$  upsurge may cause a feedforward, self-amplified loop creating cellular damage far beyond direct  $\text{Ca}^{2+}$  induced damage” [204].*

Environmental as well as genetic routes to calcium signaling dysfunction have been identified [205] including chemicals such as the polyaromatic hydrocarbons.

PCB-95 in particular modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth [206,207]. In fact, once a genetic mutation has been associated with altering a critical signaling pathway and conferring risk for autism, chemicals or other environmental agents can be identified that target the same pathways and also confer ASC risk. Stamou et al. (2012) have reviewed this strategy of identifying multiple mechanisms converging on common signaling pathways regarding Ca(2+)-dependent mechanisms as well as extracellular signal-regulated kinases (ERK)/phosphatidylinositol-3-kinases (PI3K) and neuroligin-neurexin-SHANK [208]. From this point of view, there may be no particular reason to privilege genetic mutations in their contribution to a disturbance of calcium signaling, since whether this function becomes derailed due to a genetic mutation, from a chemical toxin or from EMF/RFR perturbation of calcium signaling, the functional effect is comparable.

### 3.1.3. Junctions and barriers

The damage discussed so far has been at the molecular and subcellular level. However impacts from this level reverberate up to larger scales in the system. Where membranes create boundaries between cells and subcellular compartments, barriers do this at a larger scale. Cells become capable of forming barriers between each other through tight junctions which block substances and cells from ‘slipping through the cracks,’ so to speak, between the cells. Conversely, gap junctions are subcellular structures providing openings that allow physical passage of materials between cells otherwise separated by membranes.

Such connections between cells can also be altered by electromagnetic fields and radiofrequency exposures, at least under certain circumstances. High frequency magnetic fields have been observed to be associated with a sharp decrease in intercellular gap junction-like structures, in spite of increased gene expression for pertinent proteins [209]. Changes in tight junctions have been observed upon exposure to microwave and x-ray irradiation [210].

A number of papers in the ASC research field document problems pertinent to junctions. Connexin abnormalities have been documented in neuropathological studies [211] and MacFabe and colleagues identified lipid alterations associated with oxidative stress, membrane fluidity and the modulation of gap junction coupling [212]. Decrease in platelet endothelial cell adhesion molecule-1 were reduced and this reduction correlated with repetitive behavior and abnormal brain growth; adhesion molecules modulate permeability and signaling at the blood–brain barrier as well as leukocyte infiltration into the central nervous system [213].

EMF and RFR might also compromise biologically important barrier structures that separate blood flow from organs like the brain [214]. This raises important questions regarding whether other ‘barriers’ that keep blood flow separate from the gut (gut–blood barrier), or the placenta (blood–placenta barrier) or the eye (ocular–blood barrier) may also be

rendered pathologically leaky, and allow albumin, toxins, pro-inflammatory cytokines and infectious agents to cross these barriers, which may invoke immune responses in the intestines, and may impact the developing fetus [215]. While there are a fair number of negative studies, there are also many studies showing an association between EMF/RFR and pathological leakage of the blood–brain barrier (BBB), as well as evidence in animal studies of damage to brain cells and damage to or death of neurons. Such leakage has been shown to be potentiated by physiological factors such as diabetes and insulin (Gulturk et al., 2010) and has also potentiated viral lethality in a dose-dependent fashion (Lange et al., 1991). Many of the positive findings were associated with non-thermal exposures comparable to normal cell phone radiation exposure [216–222]. There are scattered reports of increased permeability across other membranes and barriers, such as the blood–testicle barrier in mice (Wang, 2008; Wang et al., 2010 and the rat liver canalicular membrane [223]). A 1992 study by Kues et al. reported that “*studies in our laboratory have established that pulsed microwaves at 2.45 GHz and 10 mW/cm<sup>2</sup> are associated with production of corneal endothelial lesions and with disruption of the blood–aqueous barrier in the non-human primate eye*” [224]. A recent study showing impact of high-frequency electromagnetic fields on trophoblastic connexins [209] may indicate the vulnerability of the placenta and placental barrier function to electromagnetic fields. A thorough review and methodological discussion of literature regarding EMF/RFR impacts on the BBB is provided by Salford in Section 10 of the BioInitiative 2012 Report [214].

BBB integrity can be compromised by oxidative stress which can lead to increased permeability [225], and the resultant extravasation of albumin into brain parenchyma can be excitotoxic and neurotoxic [226,227]. The interaction of these factors may contribute to a feed-forward vicious cycle that can result in progressive synaptic and neuronal dysfunction as seen in various neurodegenerative diseases [228].

The evidence suggesting possible existence of barrier function compromise in people with ASCs is largely indirect. The existence of brain neuroinflammation in ASCs has been documented in a growing number of studies [160,229,230], and this is known to be associated with BBB permeability [231–233]. In a review of clinical MRI findings in ASCs 19/59 showed white matter signal abnormalities [234], which in other settings have been associated with cerebral hypoperfusion, though not necessarily in the same locations as the hyperintensities [235,236]. Blood flow abnormalities, predominantly hypoperfusion, documented in a few dozen PET and SPECT studies, could also be caused by and/or associated with physiological phenomena associated with vascular permeability as will be revisited below. Increased intestinal permeability has been documented (although its absence has also been documented) [237–243] and discussed in the context of food exposures, particularly gluten [244–250]. The reactivity to large numbers of different foods, clinically observed in many children with autism, has been framed by



some as a manifestation of indiscriminate exposure of the immune system and the brain to food proteins on account of intestinal permeability as well as BBB permeability [251]. This reactivity could in turn feed in to aberrant immune responsiveness which in turn could further amplify barrier vulnerability [248].

A number of studies have made an association between an increased risk of having a child with autism and maternal infection during pregnancy. This phenomenon looks like it is a result of the maternal immune system response rather than being due to an impact deriving from a specific infectious agent; but the potential for an accompanying compromise of the placental barrier is also conceivable in this setting. Under these circumstances the fetal risk of exposure to maternal blood toxins, cytokines and stress proteins in utero could potentially be increased if placenta barrier (BPB) function were impaired. The integrity, or compromise thereto, of the maternal-fetal interface via the placenta is an important modulator of brain development [252].

### 3.1.4. Genetic alterations and reproductive impacts

The overwhelming emphasis in recent decades in autism research has been on genetics, and on finding linkages between genes, brain and behavior, in part because of the high heritability of autism that was calculated from the concordance rates of monozygotic (identical) vs. dizygotic (fraternal) twins found in by a series of small twin studies performed some decades ago. In recent years the genetic premises of this seemingly obvious framing of autism as overwhelmingly genetic have been undermined at several levels [253]. First, the number of reported cases is increasing, making it more difficult to maintain that ASCs are purely genetic because these increases can only be partly explained away by greater awareness or other data artifacts [254,255]. Second, the complexity of the ways we understand how genes might relate to autism has grown, from an expectation a decade ago that a small number of genes (even less than a dozen) would explain everything to an identification of close to a thousand genes associated with autism with common threads linking only a small subset [256,257], as well as ‘de novo’ mutations present in ASC children but not their parents and even ‘boutique’ mutations not shared beyond an individual family. Moreover, a recent twin study that was much larger than any of the prior such studies identified a modest genetic role but a substantial environmental role [258]. Indeed even concordance between identical twins appears to be influenced by whether the twins shared a placenta [259]. All of this calls into question the idea that genetics can be presumed to be the ‘cause’ of autism simply based upon heritability calculations, and upgrades the importance of looking not only at the environment and environmentally vulnerable physiology, but also at acquired mutations.

**3.1.4.1. Genotoxicity.** Genotoxicity has been proposed as a mechanism for the generation of ‘de novo’ mutations (found in children but not their parents) being found in

ASCs [260]. Reviews and published scientific papers on genotoxicity and EMF report that both ELF-EMF and RFR exposures are genotoxic – i.e., damaging to DNA – under certain conditions of exposure, including under conditions of intermittent and/or chronic ELF and RFR exposure that are of low-intensity and below current world safety standards [104,105,261–266]. Types of genetic damage reported have included DNA fragmentation and single- and double-strand DNA breaks, micronucleation and chromosome aberrations, all of which indicate genetic instability [102,103].

Researchers have recently identified large numbers of de novo mutations, more likely to be transmitted by fathers than by mothers to their children [267–269]. This is consistent with the EMF/RFR literature that repeatedly documents DNA damage to sperm from cell phone radiation (see Section 3.1.4.1.2). The Eichler team at the University of Washington found that 39% of the 126 most severe or disruptive mutations map to a network associated with chromatin remodeling that has already been ranked as significant amongst autism candidate genes [268]. Although the relationship between the prominence of chromatin-related gene mutations and the impacts of EMF/RFR on chromatin condensation has not been clarified, the parallels support further investigation.

#### 3.1.4.1.1. Contributors to genotoxicity.

##### • Oxidative stress and free radical damage to DNA

Oxidative stress and excessive free radical production are very well known to be potentially genotoxic. They can be a consequence of myriad environmental factors, including but by no means limited to EMF/RFR. The DNA damage that can result could very well be one cause of ‘de novo’ mutations which to date have been found in only a small percentage of individuals with ASCs. Although there is not a consensus at this time about the rates or causes of de novo mutations in ASCs, environmentally triggered oxidative stress and free radical damage that we know are present in large numbers of people with ASCs can be genotoxic, and this warrants a serious investigation of the potential contribution of EMF and RFR to de novo mutations in ASC. Further, the huge increases in exposure to EMF/RFR in daily life due to electrification and the global saturation of RFR from wireless technologies [81] reinforce this need.

##### • Challenge to DNA repair mechanisms

When the rate of damage to DNA exceeds the rate at which DNA can be repaired, there is the possibility of retaining mutations and initiating pathology. Failure to trigger DNA damage repair mechanisms, or incomplete or failed repair, may be a consequence of a variety of commonplace stressors, including EMF/RFR exposure. A decrease in DNA repair efficiency has been reported to result from exposure to low-intensity RFR in human stem cells, and other cells. Mobile phone frequency GSM exposure at the frequency of 915 MHz consistently inhibited DNA repair foci in lymphocytes [270–272]. Belyaev, Markova and colleagues (2005), and Markova et al. (2009)



reported that very low-intensity microwave radiation from mobile phones inhibits DNA repair processes in human stem cells. A significant reduction in 53BP1 (tumor suppressor p53 binding protein 1) foci was found in cells exposed to microwave radiofrequency radiation within one hour of exposure. Fibroblast cells were impacted in this fashion but adapted over time, whereas stem cells were similarly affected (inhibited 53BP1 foci) but did not adapt to microwave radiation during chronic exposure [270,271]. Additional challenges to DNA repair mechanisms include not only toxicants and other damaging inputs but also nutritional insufficiencies of substances important to the proper functioning of DNA repair mechanisms, including Vitamin D, essential fatty acids, and minerals such as selenium and molybdenum [273]. The high possibility that various such contributors may combine supports an ‘allostatic load’ model of environmental injury and genotoxicity.

#### • Chromatin condensation

The work of Markova, Belyaev and others has repeatedly shown that RFR exposure can cause chromatin condensation, which is a hallmark of DNA damage. Belyaev (1997) reported that super-low intensity RFR resulted in changes in genes, and chromatin condensation of DNA at intensities comparable to exposures from cell towers (typically at RFR levels of 0.1 to one microwatt per centimeter squared ( $\mu\text{W}/\text{cm}^2$ )) [274]. Significant microwave (MW)-induced changes in chromatin conformation were observed when rat thymocytes were analyzed between 30–60 min after exposure to MW [275].

In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to non-thermal microwave radiation (NT MW) from the GSM mobile phones [270,271]. NT MW induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. The same group has reported that contrary to human fibroblast cells, which were able to adapt during chronic exposure to GSM/UMTS low intensity RFR exposure, human stem cells did not adapt [272].

**3.1.4.1.2. Gonadal and germline impacts.** De novo mutations have been shown to be more of a problem related to paternal age [268,276–279], and this may be related to the impact of environmental factors such as EMF/RFR on the stem cell genome, particularly in sperm which have no DNA repair capacity. Vulnerability of testes and ova, and of sperm and egg cells, relates to the tissue milieu in which damage to the germline can take place, as well as on the greater vulnerability of stem cells. Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket [106,280–284]. Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure [175,284,285].

Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line [134,286–290]. Of note, altered fatty acids consistent with oxidative stress have been found in sperm cells in male infertility [291,292].

There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al. (2012) report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster* [293]. Gul et al. (2009) report rats exposed to stand-by level RFR (phones on but not transmitting calls) caused decrease in the number of ovarian follicles in pups born to these exposed dams [294]. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than  $1.0 \mu\text{W}/\text{cm}^2$  [295].

**3.1.4.1.3. Implications of genotoxicity.** The issue of genotoxicity puts the contribution of genetic variation into a different light – as something that needs to be accounted for, not necessarily assumed as the starting point. In this regard it has been speculated that the apparent higher rates of autism in Silicon Valley, discussed in the past as related to ‘geek genes’ [296], might be conditioned by higher levels of exposure to EMF/RFR. The relationship between the greater vulnerability of male sperm than of female eggs to adverse effects of EMF/RFR exposure and the marked (4:1) predominance of paternal origin of de novo point mutations (4:1 bias), also deserves further careful attention [268].

#### 3.1.5. Implications of damage

We have reviewed parallels between ASC and EMF/RFR in molecular, cellular and tissue damage, including cellular stress (oxidative stress, the heat shock response and protein misfolding), injury of membranes, aberrant calcium signaling, and compromise of cell junctions and barriers. The genotoxicity of EMF/RFR was reviewed in relation to issues of environmental contributions to autism and of the phenomenon of de novo mutations. The compromise of the tissue substrate appears to have many commonalities in ASCs and in EMF/RFR exposures. Also notable was the possibility of attenuating some of the damage through increasing antioxidant status.

Regarding Rett syndrome, a genetic syndrome often associated with autistic behaviors, these commonalities come to mind in considering the implications of a recent study documenting arrest of symptomatology in a mouse model of Rett syndrome through a bone marrow transplant of wild-type microglia [297,298]. The introduction of these competent microglia cells did not directly target the neuronal defect associated with the MECP2 gene mutation; instead the benefits of the transplant were due to overcoming the inhibition of phagocytosis caused by the MECP2 mutation that was absent in the wild-type microglia. Phagocytosis involves removing debris. This suggests that while research has focused on how

specific molecular defects, particularly in the synapse, may contribute to Rett pathophysiology, there may also be an important contribution from cellular debris, misfolded proteins and other disordered cellular structure and function. Such disorder could be accumulating in cells under the conditions of pathophysiological disarray reviewed above. Based on this study as well as on the levels of damage just reviewed, cellular problems that are pertinent to ASCs most likely go beyond any specific defect introduced by a mutation. Additionally it is conceivable that many of the mutations may be not part of normal background variation but instead collateral damage from the same environmental factors that are also driving the damage to the physiology.

### 3.1.6. Summary of Part I and preview of Part II

The data reviewed above in Part I of this two part paper documents a series of parallels between the pathophysiological and genotoxic impacts of EMF/RFR and the pathophysiological underpinnings of ASCs. DNA damage, immune and blood–brain barrier disruption, cellular and oxidative stress, calcium channel, disturbed circadian rhythms, hormone dysregulation, and degraded cognition, sleep, autonomic regulation and brainwave activity all have commonalities between ASCs and EMF/RFR, and the disruption of disruption fertility and reproduction associated with EMF/RFR may also be related to the increasing incidence of ASCs. All of this argues for reduction of exposures now, and better coordinated research in these areas.

These pathophysiological parallels are laid out after identifying the dynamic features of ASCs that could plausibly arise out of such pathophysiological dysregulation. The importance of transduction between levels was also discussed in Part I, and will be elucidated in much more detail in Part II where more detail will be given about the possible interfaces between the cellular and molecular pathophysiology reviewed above and the higher-level disruption of physiological systems, brain tissue and nervous system electrophysiology.

The emergence of ever larger amounts of data is transforming our understanding of ASCs from static encephalopathies based on genetically caused brain damage to dynamic encephalopathies where challenging behaviors emanate from physiologically disrupted systems. In parallel, the emergence of ever larger bodies of evidence supporting a large array of non-thermal but profound pathophysiological impacts of EMF/RFR is transforming our understanding of the nature of EMF/RFR impacts on the organism.

At present our policies toward ASCs are based on outdated assumptions about autism being a genetic, behavioral condition, whereas our medical, educational and public health policies related to treatment and prevention could be much more effective if we took whole-body, gene-environment considerations into account, because there are many lifestyle and environmental modifications that could reduce morbidity and probably incidence of ASCs as well.

At present our EMF/RFR standards are based on outdated purely thermal considerations, whereas the evidence is now overwhelming that limiting regulations in this way does not address the much broader array of risks and harm now known to be created by EMF/RFR.

In particular, the now well-documented genotoxic impacts of EMF/RFR, placed in parallel with the huge rise in reported cases of ASCs as well as with the de novo mutations associated with some cases of ASCs (as well as other conditions), make it urgent for us to place the issue of acquired as well as inherited genetic damage on the front burner for scientific investigation and policy remediation.

With the rising numbers people with ASCs and other childhood health and developmental disorders, and with the challenges to our prior assumptions posed ever more strongly by emerging evidence, we need to look for and act upon risk factors that are largely avoidable or preventable. We would argue that the evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels causing biological disruption and strong, interim precautionary practices are advocated. Further evidence to support the pathophysiological support for parallels between ASCs and EMF/RFR impacts and for taking action will be offered in Part II.

## References

- [1] M. Blank, in: O. Hanninen (Ed.), *Electromagnetic Fields, Pathophysiology*, 2009.
- [2] C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012, A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012, <http://www.bioinitiative.org/>
- [3] International Commission for Electromagnetic Safety (ICEMS), *Non-thermal effects and mechanisms of interaction between electromagnetic fields and living matter*, Eur. J. Oncol. Libr. 5 (2010).
- [4] Interphone Study Group, *Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study*, Int. J. Epidemiol. 39 (2010) 675–694.
- [5] R. Baan, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, F. Islami, L. Galichet, K. Straif, *Carcinogenicity of radiofrequency electromagnetic fields*, Lancet Oncol. 12 (2011) 624–626.
- [6] N.R.C. Committee on Identification of Research Needs Relating to Potential Biological or Adverse Health Effects of Wireless Communications Devices, *Identification of Research Needs Relating to Potential Biological or Adverse Health Effects of Wireless Communication*, 2008.
- [7] M.R. Herbert, C. Sage, in: C. Sage, D.O. Carpenter (Eds.), *Findings in Autism Spectrum Disorders consistent with Electromagnetic Frequencies (EMF) and Radiofrequency Radiation (RFR)*, BioInitiative Update, 2012, [www.BioInitiative.org](http://www.BioInitiative.org)
- [8] L. Kanner, *Autistic disturbances of affective contact*, Nerv. Child 2 (1943) 217–250 (reprint in Acta Paedopsychiatr. 35 (4) (1968) 100–136. PMID 4880460).
- [9] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision)*, American Psychiatric Publishing, Arlington, VA, 2000.
- [10] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders DSM-v*, American Psychiatric Publishing, Arlington, VA, 2013, May.

- [11] M.R. Herbert, Autism: a brain disorder or a disorder that affects the brain? *Clin. Neuropsychiatry* 2 (2005) 354–379, <http://www.marthahebert.com/publications>
- [12] I. Rapin, R. Katzman, Neurobiology of autism, *Ann. Neurol.* 43 (1998) 7–14.
- [13] F. Polleux, J.M. Lauder, Toward a developmental neurobiology of autism, *Ment. Retard. Dev. Disabil. Res. Rev.* 10 (2004) 303–317.
- [14] X. Ming, T.P. Stein, V. Barnes, N. Rhodes, L. Guo, Metabolic perturbation in autism spectrum disorders: a metabolomics study, *J. Proteome Res.* 11 (2012) 5856–5862.
- [15] S. Tsaluchidu, M. Cocchi, L. Tonello, B.K. Puri, Fatty acids and oxidative stress in psychiatric disorders, *BMC Psychiatry* 8 (Suppl. 1) (2008) S5.
- [16] S.R. Pieczenik, J. Neustadt, Mitochondrial dysfunction and molecular pathways of disease, *Exp. Mol. Pathol.* 83 (2007) 84–92.
- [17] A. Gonzalez, J. Stombaugh, C. Lozupone, P.J. Turnbaugh, J.I. Gordon, R. Knight, The mind–body–microbial continuum, *Dialogues Clin. Neurosci.* 13 (2011) 55–62.
- [18] R.N. Nikolov, K.E. Bearss, J. Lettinga, C. Erickson, M. Rodowski, M.G. Aman, J.T. McCracken, C.J. McDougle, E. Tierney, B. Vitiello, L.E. Arnold, B. Shah, D.J. Posey, L. Ritz, L. Seahill, Gastrointestinal symptoms in a sample of children with pervasive developmental disorders, *J. Autism Dev. Disord.* 39 (2009) 405–413.
- [19] S. Kotagal, E. Broomall, Sleep in children with autism spectrum disorder, *Pediatr. Neurol.* 47 (2012) 242–251.
- [20] M. Kaartinen, K. Puura, T. Makela, M. Rannisto, R. Lemponen, M. Helminen, R. Salmelin, S.L. Himanen, J.K. Hietanen, Autonomic arousal to direct gaze correlates with social impairments among children with ASD, *J. Autism Dev. Disord.* 42 (2012) 1917–1927.
- [21] C. Daluwatte, J.H. Miles, S.E. Christ, D.Q. Beversdorf, T.N. Takahashi, G. Yao, Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder, *J. Autism Dev. Disord.* 43 (2013) 1910–1925.
- [22] R. Tuchman, M. Cuccaro, Epilepsy and autism: neurodevelopmental perspective, *Curr. Neurol. Neurosci. Rep.* 11 (2011) 428–434.
- [23] R. Canitano, Epilepsy in autism spectrum disorders, *Eur. Child Adolesc. Psychiatry* 16 (2007) 61–66.
- [24] B.A. Malow, Sleep disorders, epilepsy, and autism, *Ment. Retard. Dev. Disabil. Res. Rev.* 10 (2004) 122–125.
- [25] J.Q. Kang, G. Barnes, A common susceptibility factor of both autism and epilepsy: functional deficiency of GABA(A) receptors, *J. Autism Dev. Disord.* 43 (2013) 68–79.
- [26] H. Jyonouchi, L. Geng, D.L. Streck, G.A. Toruner, Children with autism spectrum disorders (ASD) who exhibit chronic gastrointestinal (GI) symptoms and marked fluctuation of behavioral symptoms exhibit distinct innate immune abnormalities and transcriptional profiles of peripheral blood (PB) monocytes, *J. Neuroimmunol.* 238 (2011) 73–80.
- [27] I.S. Kohane, A. McMurry, G. Weber, D. Macfadden, L. Rappaport, L. Kunkel, J. Bickel, N. Wattanasin, S. Spence, S. Murphy, S. Churchill, The co-morbidity burden of children and young adults with autism spectrum disorders, *PLoS ONE* 7 (2012) e33224.
- [28] T.A. Trikalinos, A. Karvouni, E. Zintzaras, T. Ylisaukko-oja, L. Peltonen, I. Jarvela, J.P. Ioannidis, A heterogeneity-based genome search meta-analysis for autism-spectrum disorders, *Mol. Psychiatry* 11 (2006) 29–36.
- [29] H. Ring, M. Woodbury-Smith, P. Watson, S. Wheelwright, S. Baron-Cohen, Clinical heterogeneity among people with high functioning autism spectrum conditions: evidence favouring a continuous severity gradient, *Behav. Brain Funct.* 4 (2008) 11.
- [30] K.A. Pelphrey, S. Shultz, C.M. Hudac, B.C. Vander Wyk, Research review: constraining heterogeneity: the social brain and its development in autism spectrum disorder, *J. Child Psychol. Psychiatry* 52 (2011) 631–644.
- [31] D. Mandell, The heterogeneity in clinical presentation among individuals on the autism spectrum is a remarkably puzzling facet of this set of disorders, *Autism* 15 (2011) 259–261.
- [32] D. Hall, M.F. Huerta, M.J. McAuliffe, G.K. Farber, Sharing heterogeneous data: the national database for autism research, *Neuroinformatics* 10 (2012) 331–339.
- [33] B.R. Bill, D.H. Geschwind, Genetic advances in autism: heterogeneity and convergence on shared pathways, *Curr. Opin. Genet. Dev.* 19 (2009) 271–278.
- [34] A.J. Whitehouse, B.J. Holt, M. Serralha, P.G. Holt, P.H. Hart, M.M. Kusel, Maternal vitamin D levels and the autism phenotype among offspring, *J. Autism Dev. Disord.* 43 (2013) 1495–1504.
- [35] E. Kocovska, E. Fernell, E. Billstedt, H. Minnis, C. Gillberg, Vitamin D and autism: clinical review, *Res. Dev. Disabil.* 33 (2012) 1541–1550.
- [36] R.J. Schmidt, R.L. Hansen, J. Hartiala, H. Allayee, L.C. Schmidt, D.J. Tancredi, F. Tassone, I. Hertz-Picciotto, Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism, *Epidemiology* 22 (2011) 476–485.
- [37] P.J. Landrigan, What causes autism? Exploring the environmental contribution, *Curr. Opin. Pediatr.* 22 (2010) 219–225.
- [38] E.M. Roberts, P.B. English, J.K. Grether, G.C. Windham, L. Somberg, C. Wolff, Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley, *Environ. Health Perspect.* 115 (10) (2007 Oct) 1482–1489.
- [39] J.F. Shelton, I. Hertz-Picciotto, I.N. Pessah, Tipping the balance of autism risk: potential mechanisms linking pesticides and autism, *Environ. Health Perspect.* 120 (2012) 944–951.
- [40] T.A. Becerra, M. Wilhelm, J. Olsen, M. Cockburn, B. Ritz, Ambient air pollution and autism in Los Angeles County, California, *Environ. Health Perspect.* 121 (2013) 380–386.
- [41] H.E. Volk, I. Hertz-Picciotto, L. Delwiche, F. Lurmann, R. McConnell, Residential proximity to freeways and autism in the CHARGE study, *Environ. Health Perspect.* 119 (2011) 873–877.
- [42] S.D. Bilbo, J.P. Jones, W. Parker, Is autism a member of a family of diseases resulting from genetic/cultural mismatches? Implications for treatment and prevention, *Autism Res. Treat.* 2012 (2012) 910946.
- [43] S.S. Knox, From ‘omics’ to complex disease: a systems biology approach to gene–environment interactions in cancer, *Cancer Cell Int.* 10 (2010) 11.
- [44] M.R. Herbert, Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders, *Curr. Opin. Neurol.* 23 (2010) 103–110.
- [45] H. Wei, K.K. Chadman, D.P. McCloskey, A.M. Sheikh, M. Malik, W.T. Brown, X. Li, Brain IL-6 elevation causes neuronal circuitry imbalances and mediates autism-like behaviors, *Biochim. Biophys. Acta* 1822 (2012) 831–842.
- [46] M. Careaga, P. Ashwood, Autism spectrum disorders: from immunity to behavior, *Methods Mol. Biol.* 934 (2012) 219–240.
- [47] P. Ashwood, P. Krakowiak, I. Hertz-Picciotto, R. Hansen, I. Pessah, J. Van de Water, Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome, *Brain Behav. Immun.* 25 (2011) 40–45.
- [48] L. Heuer, P. Ashwood, J. Schauer, P. Goines, P. Krakowiak, I. Hertz-Picciotto, R. Hansen, L.A. Croen, I.N. Pessah, J. Van de Water, Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms, *Autism Res.* 1 (2008) 275–283.
- [49] M.C. Zerrate, M. Pletnikov, S.L. Connors, D.L. Vargas, F.J. Seidler, A.W. Zimmerman, T.A. Slotkin, C.A. Pardo, Neuroinflammation and behavioral abnormalities after neonatal terbutaline treatment in rats: implications for autism, *J. Pharmacol. Exp. Ther.* 322 (2007) 16–22.
- [50] L.K. Curran, C.J. Newschaffer, L.C. Lee, S.O. Crawford, M.V. Johnston, A.W. Zimmerman, Behaviors associated with fever in children with autism spectrum disorders, *Pediatrics* 120 (2007) e1386–e1392.



- [51] M. Helt, E. Kelley, M. Kinsbourne, J. Pandey, H. Boorstein, M. Herbert, D. Fein, Can children with autism recover? If so, how? *Neuropsychol. Rev.* 18 (2008) 339–366.
- [52] S. Cobb, J. Guy, A. Bird, Reversibility of functional deficits in experimental models of Rett syndrome, *Biochem. Soc. Trans.* 38 (2010) 498–506.
- [53] D. Ehninger, S. Han, C. Shilyansky, Y. Zhou, W. Li, D.J. Kwiatkowski, V. Ramesh, A.J. Silva, Reversal of learning deficits in a Tsc2+/- mouse model of tuberous sclerosis, *Nat. Med.* 14 (2008) 843–848.
- [54] S.M. Goebel-Goody, E.D. Wilson-Wallis, S. Royston, S.M. Tagliatela, J.R. Naegel, P.J. Lombroso, Genetic manipulation of STEP reverses behavioral abnormalities in a fragile X syndrome mouse model, *Genes Brain Behav.* 11 (2012) 586–600.
- [55] C. Henderson, L. Wijetunge, M.N. Kinoshita, M. Shumway, R.S. Hammond, F.R. Postma, C. Brynczka, R. Rush, A. Thomas, R. Paylor, S.T. Warren, P.W. Vanderklisch, P.C. Kind, R.L. Carpenter, M.F. Bear, A.M. Healy, Reversal of disease-related pathologies in the fragile X mouse model by selective activation of GABA(B) receptors with arbaclofen, *Sci. Transl. Med.* 4 (2012) 152ra128.
- [56] H. Kaphzan, P. Hernandez, J.I. Jung, K.K. Cowansage, K. Deinhardt, M.V. Chao, T. Abel, E. Klann, Reversal of impaired hippocampal long-term potentiation and contextual fear memory deficits in Angelman syndrome model mice by ErbB inhibitors, *Biol. Psychiatry* 72 (2012) 182–190.
- [57] Z.H. Liu, T. Huang, C.B. Smith, Lithium reverses increased rates of cerebral protein synthesis in a mouse model of fragile X syndrome, *Neurobiol. Dis.* 45 (2012) 1145–1152.
- [58] M.V. Mehta, M.J. Gandal, S.J. Siegel, mGluR5-antagonist mediated reversal of elevated stereotyped, repetitive behaviors in the VPA model of autism, *PLoS ONE* 6 (2011) e26077.
- [59] R. Paylor, L.A. Yuva-Paylor, D.L. Nelson, C.M. Spencer, Reversal of sensorimotor gating abnormalities in Fmr1 knockout mice carrying a human Fmr1 transgene, *Behav. Neurosci.* 122 (2008) 1371–1377.
- [60] S.E. Rotschafer, M.S. Trujillo, L.E. Dansie, I.M. Ethell, K.A. Razak, Minocycline treatment reverses ultrasonic vocalization production deficit in a mouse model of Fragile X Syndrome, *Brain Res.* 1439 (2012) 7–14.
- [61] A. Sato, S. Kasai, T. Kobayashi, Y. Takamatsu, O. Hino, K. Ikeda, M. Mizuguchi, Rapamycin reverses impaired social interaction in mouse models of tuberous sclerosis complex, *Nat. Commun.* 3 (2012) 1292.
- [62] A. Suvrathan, C.A. Hoeffer, H. Wong, E. Klann, S. Chattarji, Characterization and reversal of synaptic defects in the amygdala in a mouse model of fragile X syndrome, *Proc. Natl. Acad. Sci. U. S. A.* 107 (2010) 11591–11596.
- [63] A. Narayanan, C.A. White, S. Saklayen, M.J. Scaduto, A.L. Carpenter, A. Abduljalil, P. Schmalbrock, D.Q. Beversdorf, Effect of propranolol on functional connectivity in autism spectrum disorder – a pilot study, *Brain Imaging Behav.* 4 (2010) 189–197.
- [64] R.H. Sandler, S.M. Finegold, E.R. Bolte, C.P. Buchanan, A.P. Maxwell, M.L. Vaisanen, M.N. Nelson, H.M. Wexler, Short-term benefit from oral vancomycin treatment of regressive-onset autism, *J. Child Neurol.* 15 (2000) 429–435.
- [65] M.R. Herbert, Autism: The Centrality of Active Pathophysiology and the Shift from Static to Chronic Dynamic Encephalopathy, Taylor & Francis/CRC Press, 2009.
- [66] M.E. Edelson, Are the majority of children with autism mentally retarded? A systematic evaluation of the data, *Focus Autism Other Dev. Disabil.* 21 (2006) 66–82.
- [67] M. Dawson, I. Soulières, M.A. Gernsbacher, L. Mottron, The level and nature of autistic intelligence, *Psychol. Sci.* 18 (2007) 657–662.
- [68] I. Soulières, T.A. Zeffiro, M.L. Girard, L. Mottron, Enhanced mental image mapping in autism, *Neuropsychologia* 49 (2011) 848–857.
- [69] I. Soulières, M. Dawson, M.A. Gernsbacher, L. Mottron, The level and nature of autistic intelligence II: what about Asperger syndrome? *PLoS ONE* 6 (2011) e25372.
- [70] F. Samson, L. Mottron, I. Soulières, T.A. Zeffiro, Enhanced visual functioning in autism: an ALE meta-analysis, *Hum. Brain Mapp.* 33 (2012) 1553–1581.
- [71] I. Soulières, B. Hubert, N. Rouleau, L. Gagnon, P. Tremblay, X. Seron, L. Mottron, Superior estimation abilities in two autistic spectrum children, *Cogn. Neuropsychol.* 27 (2010) 261–276.
- [72] I. Soulières, M. Dawson, F. Samson, E.B. Barbeau, C.P. Sahyoun, G.E. Strangman, T.A. Zeffiro, L. Mottron, Enhanced visual processing contributes to matrix reasoning in autism, *Hum. Brain Mapp.* 30 (2009) 4082–4107.
- [73] L. Mottron, M. Dawson, I. Soulières, B. Hubert, J. Burack, Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception, *J. Autism Dev. Disord.* 36 (2006) 27–43.
- [74] L. Mottron, Matching strategies in cognitive research with individuals with high-functioning autism: current practices, instrument biases, and recommendations, *J. Autism Dev. Disord.* 34 (2004) 19–27.
- [75] A. Bertone, L. Mottron, P. Jelenic, J. Faubert, Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity, *Brain* 128 (2005) 2430–2441.
- [76] A. Perreault, R. Gurnsey, M. Dawson, L. Mottron, A. Bertone, Increased sensitivity to mirror symmetry in autism, *PLoS ONE* 6 (2011) e19519.
- [77] M. Korson, Intermittent autism in patients with mitochondrial disease, in: *Autism: Genes, Brains, Babies and Beyond*, Massachusetts General Hospital, 2007.
- [78] M.R. Herbert, K. Weintraub, *The Autism Revolution: Whole Body Strategies for Making Life All It Can Be*, Random House with Harvard Health Publications, New York, NY, 2012.
- [79] B.S. McEwen, Stress, adaptation, and disease. Allostasis and allostatic load, *Ann. N. Y. Acad. Sci.* 840 (1998) 33–44.
- [80] J. Juutilainen, T. Kumlin, J. Naarala, Do extremely low frequency magnetic fields enhance the effects of environmental carcinogens? A meta-analysis of experimental studies, *Int. J. Radiat. Biol.* 82 (2006) 1–12.
- [81] C. Sage, D. Carpenter, Key scientific evidence and public health policy recommendations, in: *The BioInitiative Report 2012: A Rationale for a Biologically-Based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012, <http://www.bioinitiative.org/table-of-contents/>
- [82] C. Lintas, R. Sacco, A.M. Persico, Genome-wide expression studies in autism spectrum disorder, Rett syndrome, and Down syndrome, *Neurobiol. Dis.* 45 (2012) 57–68.
- [83] S.W. Kong, C.D. Collins, Y. Shimizu-Motohashi, I.A. Holm, M.G. Campbell, I.H. Lee, S.J. Brewster, E. Hanson, H.K. Harris, K.R. Lowe, A. Saada, A. Mora, K. Madison, R. Hundley, J. Egan, J. McCarthy, A. Eran, M. Galdzicki, L. Rappaport, L.M. Kunkel, I.S. Kohane, Characteristics and predictive value of blood transcriptome signature in males with autism spectrum disorders, *PLoS ONE* 7 (2012) e49475.
- [84] J.Y. Jung, I.S. Kohane, D.P. Wall, Identification of autoimmune gene signatures in autism, *Transl. Psychiatry* 1 (2011) e63.
- [85] I. Voineagu, X. Wang, P. Johnston, J.K. Lowe, Y. Tian, S. Horvath, J. Mill, R.M. Cantor, B.J. Blencowe, D.H. Geschwind, Transcriptomic analysis of autistic brain reveals convergent molecular pathology, *Nature* 474 (2011) 380–384.
- [86] M.I. Waly, M. Hornig, M. Trivedi, N. Hodgson, R. Kini, A. Ohta, R. Deth, Prenatal and postnatal epigenetic programming: implications for Gi, immune, and neuronal function in autism, *Autism Res. Treat.* 2012 (2012) 190930.
- [87] A. Kanthasamy, H. Jin, V. Anantharam, G. Sondarva, V. Rangasamy, A. Rana, Emerging neurotoxic mechanisms in environmental factors-induced neurodegeneration, *Neurotoxicology* 33 (2012) 833–837.
- [88] R.A. Roberts, R.A. Smith, S. Safe, C. Szabo, R.B. Tjalkens, F.M. Robertson, Toxicological and pathophysiological roles of reactive oxygen and nitrogen species, *Toxicology* 276 (2010) 85–94.
- [89] S. Rose, S. Melnyk, T.A. Trusty, O. Pavliv, L. Seidel, J. Li, T. Nick, S.J. James, Intracellular and extracellular redox status and free

- radical generation in primary immune cells from children with autism, *Autism Res. Treat.* 2012 (2012) 986519.
- [90] S. Rose, S. Melnyk, O. Pavliv, S. Bai, T.G. Nick, R.E. Frye, S.J. James, Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain, *Transl. Psychiatry* 2 (2012) e134.
- [91] A. Ghanizadeh, S. Akhondzadeh, Hormozi, A. Makarem, M. Abotorabi, A. Firoozabadi, Glutathione-related factors and oxidative stress in autism, a review, *Curr. Med. Chem.* 19 (2012) 4000–4005.
- [92] A. Frustaci, M. Neri, A. Cesario, J.B. Adams, E. Domenici, B. Dalla Bernardina, S. Bonassi, Oxidative stress-related biomarkers in autism: systematic review and meta-analyses, *Free Radic. Biol. Med.* 52 (2012) 2128–2141.
- [93] D.A. Rossignol, R.E. Frye, A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures, *Mol. Psychiatry* 17 (2012) 389–401.
- [94] J.B. Adams, T. Audhya, S. McDonough-Means, R.A. Rubin, D. Quig, E. Geis, E. Gehn, M. Loresto, J. Mitchell, S. Atwood, S. Barnhouse, W. Lee, Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity, *Nutr. Metab. (Lond.)* 8 (2011) 34.
- [95] J.B. Adams, T. Audhya, S. McDonough-Means, R.A. Rubin, D. Quig, E. Geis, E. Gehn, M. Loresto, J. Mitchell, S. Atwood, S. Barnhouse, W. Lee, Effect of a vitamin/mineral supplement on children and adults with autism, *BMC Pediatr.* 11 (2011) 111.
- [96] G.A. Mostafa, E.S. El-Hadidi, D.H. Hewedi, M.M. Abdou, Oxidative stress in Egyptian children with autism: relation to autoimmunity, *J. Neuroimmunol.* 219 (2010) 114–118.
- [97] N. Zecavati, S.J. Spence, Neurometabolic disorders and dysfunction in autism spectrum disorders, *Curr. Neurol. Neurosci. Rep.* 9 (2009) 129–136.
- [98] Y. Yao, W.J. Walsh, W.R. McGinnis, D. Pratico, Altered vascular phenotype in autism: correlation with oxidative stress, *Arch. Neurol.* 63 (2006) 1161–1164.
- [99] R.K. Naviaux, Oxidative shielding or oxidative stress? *J. Pharmacol. Exp. Ther.* 342 (2012) 608–618.
- [100] A. Chauhan, V. Chauhan, Oxidative stress in autism, *Pathophysiology* 13 (2006) 171–181.
- [101] A. Chauhan, V. Chauhan, T. Brown, *Autism: Oxidative Stress, Inflammation and Immune Abnormalities*, Taylor & Francis/CRC Press, Boca Raton, FL, 2009.
- [102] H. Lai, Evidence for genotoxic effects – RFR and ELF DNA damage (section 6), in: *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012, <http://www.bioinitiative.org/table-of-contents/>
- [103] H. Lai, Evidence for genotoxic effects – RFR and ELF DNA damage (section 6), in: *The BioInitiative Report 2012: A Rationale for a Biologically-Based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2007, <http://bioinitiative.org/freeaccess/report/index.htm>
- [104] J.L. Phillips, N.P. Singh, H. Lai, Electromagnetic fields and DNA damage, *Pathophysiology* 16 (2009) 79–88.
- [105] H. Lai, N.P. Singh, Magnetic-field-induced DNA strand breaks in brain cells of the rat, *Environ. Health Perspect.* 112 (2004) 687–694.
- [106] G.N. De Iuliis, R.J. Newey, B.V. King, R.J. Aitken, Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro, *PLoS ONE* 4 (2009) e6446.
- [107] R. Bristot Silvestrin, V. Bambini-Junior, F. Galland, L. Daniele Bobermim, A. Quincozes-Santos, R. Torres Abib, C. Zanutto, C. Batassini, G. Brolese, C.A. Goncalves, R. Riesgo, C. Gottfried, Animal model of autism induced by prenatal exposure to valproate: altered glutamate metabolism in the hippocampus, *Brain Res.* 1495 (2013) 52–60.
- [108] M.S. Brown, D. Singel, S. Hepburn, D.C. Rojas, Increased glutamate concentration in the auditory cortex of persons with autism and first-degree relatives: a (1) H-MRS study, *Autism Res.* 6 (2013) 1–10.
- [109] P.R. Choudhury, S. Lahiri, U. Rajamma, Glutamate mediated signaling in the pathophysiology of autism spectrum disorders, *Pharmacol. Biochem. Behav.* 100 (2012) 841–849.
- [110] M.M. Essa, N. Braidy, K.R. Vijayan, S. Subash, G.J. Guillemin, Excitotoxicity in the pathogenesis of autism, *Neurotox. Res.* 23 (2013) 393–400.
- [111] L.M. Oberman, mGluR antagonists and GABA agonists as novel pharmacological agents for the treatment of autism spectrum disorders, *Expert Opin. Investig. Drugs* 21 (2012) 1819–1825.
- [112] Y. Yang, C. Pan, Role of metabotropic glutamate receptor 7 in autism spectrum disorders: a pilot study, *Life Sci.* 92 (2013) 149–153.
- [113] A. Chauhan, T. Audhya, V. Chauhan, Brain region-specific glutathione redox imbalance in autism, *Neurochem. Res.* 37 (2012) 1681–1689.
- [114] P.A. Main, M.T. Angley, C.E. O'Doherty, P. Thomas, M. Fenech, The potential role of the antioxidant and detoxification properties of glutathione in autism spectrum disorders: a systematic review and meta-analysis, *Nutr. Metab. (Lond.)* 9 (2012) 35.
- [115] A. Pecorelli, S. Leoncini, C. De Felice, C. Signorini, C. Cerrone, G. Valacchi, L. Ciccoli, J. Hayek, Non-protein-bound iron and 4-hydroxynonenal protein adducts in classic autism, *Brain Dev.* 35 (2013) 146–154.
- [116] A. Banerjee, F. Garcia-Oscos, S. Roychowdhury, L.C. Galindo, S. Hall, M.P. Kilgard, M. Atzori, Impairment of cortical GABAergic synaptic transmission in an environmental rat model of autism, *Int. J. Neuropsychopharmacol.* (2012) 1–10.
- [117] S. Coghlán, J. Horder, B. Inkster, M.A. Mendez, D.G. Murphy, D.J. Nutt, GABA system dysfunction in autism and related disorders: from synapse to symptoms, *Neurosci. Biobehav. Rev.* 36 (2012) 2044–2055.
- [118] P.G. Enticott, H.A. Kennedy, N.J. Rinehart, B.J. Tonge, J.L. Bradshaw, P.B. Fitzgerald, GABAergic activity in autism spectrum disorders: an investigation of cortical inhibition via transcranial magnetic stimulation, *Neuropharmacology* 68 (2013) 202–209.
- [119] M.A. Mendez, J. Horder, J. Myers, S. Coghlán, P. Stokes, D. Erritzoe, O. Howes, A. Lingford-Hughes, D. Murphy, D. Nutt, The brain GABA-benzodiazepine receptor alpha-5 subtype in autism spectrum disorder: a pilot [(11)C]Ro15-4513 positron emission tomography study, *Neuropharmacology* 68 (2013) 195–201.
- [120] A. Piton, L. Jouan, D. Rochefort, S. Dobrzaniecka, K. Lachapelle, P.A. Dion, J. Gauthier, G.A. Rouleau, Analysis of the effects of rare variants on splicing identifies alterations in GABA(A) receptor genes in autism spectrum disorder individuals, *Eur. J. Hum. Genet. EJHG* 21 (2013) 749–756.
- [121] A. Anitha, K. Nakamura, I. Thanseem, H. Matsuzaki, T. Miyachi, M. Tsujii, Y. Iwata, K. Suzuki, T. Sugiyama, N. Mori, Downregulation of the expression of mitochondrial electron transport complex genes in autism brains, *Brain Pathol.* 23 (2013) 294–302.
- [122] A. Anitha, K. Nakamura, I. Thanseem, K. Yamada, Y. Iwayama, T. Toyota, H. Matsuzaki, T. Miyachi, S. Yamada, M. Tsujii, K.J. Tsuchiya, K. Matsumoto, Y. Iwata, K. Suzuki, H. Ichikawa, T. Sugiyama, T. Yoshikawa, N. Mori, Brain region-specific altered expression and association of mitochondria-related genes in autism, *Mol. Autism* 3 (2012) 12.
- [123] J. Gargus, I. Faiqa, Mitochondrial energy-deficient endophenotype in autism, *Am. J. Biochem. Biotechnol.* 4 (2008) 198–207.
- [124] C. Giulivi, Y.F. Zhang, A. Omanska-Klusek, C. Ross-Inta, S. Wong, I. Hertz-Picciotto, F. Tassone, I.N. Pessah, Mitochondrial dysfunction in autism, *JAMA* 304 (2010) 2389–2396.
- [125] A. Hadjixenofontos, M.A. Schmidt, P.L. Whitehead, I. Konidari, D.J. Hedges, H.H. Wright, R.K. Abramson, R. Menon, S.M. Williams, M.L. Cuccaro, J.L. Haines, J.R. Gilbert, M.A. Pericak-Vance, E.R. Martin, J.L. McCauley, Evaluating mitochondrial DNA

- variation in autism spectrum disorders, *Ann. Hum. Genet.* 77 (2013) 9–21.
- [126] V. Napolioni, A.M. Persico, V. Porcelli, L. Palmieri, The mitochondrial aspartate/glutamate carrier AGC1 and calcium homeostasis: physiological links and abnormalities in autism, *Mol. Neurobiol.* 44 (2011) 83–92.
- [127] D.A. Rossignol, R.E. Frye, Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis, *Mol. Psychiatry* 17 (2012) 290–314.
- [128] A. Campisi, M. Gulino, R. Acquaviva, P. Bellia, G. Raciti, R. Grasso, F. Musumeci, A. Vanella, A. Triglia, Reactive oxygen species levels and DNA fragmentation on astrocytes in primary culture after acute exposure to low intensity microwave electromagnetic field, *Neurosci. Lett.* 473 (2010) 52–55.
- [129] A.F. Fragopoulou, A. Samara, M.H. Antonelou, A. Xanthopoulou, A. Papadopoulou, K. Vougas, E. Koutsogiannopoulou, E. Anastasiadou, D.J. Stravopodis, G.T. Tsangaris, L.H. Margaritis, Brain proteome response following whole body exposure of mice to mobile phone or wireless DECT base radiation, *Electromagn. Biol. Med.* 31 (2012) 250–274.
- [130] M. Shapiro, G. Akiri, C. Chin, J.P. Wisnivesky, M.B. Beasley, T.S. Weiser, S.J. Swanson, S.A. Aaronson, Wnt pathway activation predicts increased risk of tumor recurrence in patients with stage I nonsmall cell lung cancer, *Ann. Surg.* 257 (2013) 548–554.
- [131] E. Ozgur, G. Guler, N. Seyhan, Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants N-acetyl cysteine and epigallocatechin-gallate, *Int. J. Radiat. Biol.* 86 (2010) 935–945.
- [132] F. Ozguner, A. Altinbas, M. Ozaydin, A. Dogan, H. Vural, A.N. Kisioglu, G. Cesur, N.G. Yildirim, Mobile phone-induced myocardial oxidative stress: protection by a novel antioxidant agent caffeic acid phenethyl ester, *Toxicol. Ind. Health* 21 (2005) 223–230.
- [133] Y.M. Moustafa, R.M. Moustafa, A. Belacy, S.H. Abou-El-Ela, F.M. Ali, Effects of acute exposure to the radiofrequency fields of cellular phones on plasma lipid peroxide and antioxidant activities in human erythrocytes, *J. Pharm. Biomed. Anal.* 26 (2001) 605–608.
- [134] K.K. Kesari, S. Kumar, J. Behari, Effects of radiofrequency electromagnetic wave exposure from cellular phones on the reproductive pattern in male Wistar rats, *Appl. Biochem. Biotechnol.* 164 (2011) 546–559.
- [135] G. Jelodar, A. Akbari, S. Nazifi, The prophylactic effect of vitamin C on oxidative stress indexes in rat eyes following exposure to radiofrequency wave generated by a BTS antenna model, *Int. J. Radiat. Biol.* 89 (2013) 128–131.
- [136] A. Hoyto, J. Luukkonen, J. Juutilainen, J. Naarala, Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants, *Radiat. Res.* 170 (2008) 235–243.
- [137] M. Guney, F. Ozguner, B. Oral, N. Karahan, T. Mungan, 900 MHz radiofrequency-induced histopathologic changes and oxidative stress in rat endometrium: protection by vitamins E and C, *Toxicol. Ind. Health* 23 (2007) 411–420.
- [138] M.A. Esmekeya, C. Ozer, N. Seyhan, 900 MHz pulse-modulated radiofrequency radiation induces oxidative stress on heart, lung, testis and liver tissues, *Gen. Physiol. Biophys.* 30 (2011) 84–89.
- [139] H.I. Atasoy, M.Y. Gunal, P. Atasoy, S. Elgun, G. Bugdayci, Immunohistopathologic demonstration of deleterious effects on growing rat testes of radiofrequency waves emitted from conventional Wi-Fi devices, *J. Pediatr. Urol.* 9 (2013) 223–229.
- [140] M. Al-Demegh, Rat testicular impairment induced by electromagnetic radiation from a conventional cellular telephone and the protective effects of the antioxidants vitamins C and E, *Clinics* 67 (2012) 785–792.
- [141] G. Kumar, Report on cell tower radiation submitted to Secretary, DOT, Delhi, Electrical Engineering Dept, IIT Bombay, Powai, Mumai, 2010, December, [gkumar@ee.iitb.ac.in](mailto:gkumar@ee.iitb.ac.in)
- [142] I. Meral, H. Mert, N. Mert, Y. Deger, I. Yoruk, A. Yetkin, S. Keskin, Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs, *Brain Res.* 1169 (2007) 120–124.
- [143] F. Oktem, F. Ozguner, H. Mollaoglu, A. Koyu, E. Uz, Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone: protection by melatonin, *Arch. Med. Res.* 36 (2005) 350–355.
- [144] F. Ozguner, Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study, *Mol. Cell. Biochem.* 282 (2006) 83–88.
- [145] D.H. Lee, D.R. Jacobs Jr., M. Porta, Hypothesis: a unifying mechanism for nutrition and chemicals as lifelong modulators of DNA hypomethylation, *Environ. Health Perspect.* 117 (2009) 1799–1802.
- [146] A. Ilhan, A. Gurel, F. Armutcu, S. Kamisli, M. Iraz, O. Akyol, S. Ozen, Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain, *Clin. Chim. Acta* 340 (2004) 153–162.
- [147] I. Belyaev, Evidence for disruption by modulation: role of physical and biological variables in bioeffects of non-thermal microwaves for reproducibility, cancer risk and safety standards, in: C. Sage (Ed.), *BioInitiative 2012: A Rationale for a Biologically-Based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012.
- [148] D. Weisbrot, H. Lin, L. Ye, M. Blank, R. Goodman, Effects of mobile phone radiation on reproduction and development in *Drosophila melanogaster*, *J. Cell. Biochem.* 89 (2003) 48–55.
- [149] S. Velizarov, P. Raskmark, S. Kwee, The effects of radiofrequency fields on cell proliferation are non-thermal, *Bioelectrochem. Bioenerg.* 48 (1999) 177–180.
- [150] D. Leszczynski, R. Nylund, S. Joenvaara, J. Reivinen, Applicability of discovery science approach to determine biological effects of mobile phone radiation, *Proteomics* 4 (2004) 426–431.
- [151] D. Leszczynski, S. Joenvaara, J. Reivinen, R. Kuokka, Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: molecular mechanism for cancer- and blood-brain barrier-related effects, *Differentiation* 70 (2002) 120–129.
- [152] D. de Pomerai, C. Daniells, H. David, J. Allan, I. Duce, M. Mutwakil, D. Thomas, P. Sewell, J. Tattersall, D. Jones, P. Candido, Non-thermal heat-shock response to microwaves, *Nature* 405 (2000) 417–418.
- [153] C. Daniells, I. Duce, D. Thomas, P. Sewell, J. Tattersall, D. de Pomerai, Transgenic nematodes as biomonitors of microwave-induced stress, *Mutat. Res.* 399 (1998) 55–64.
- [154] M. Blank, R. Goodman, Comment: a biological guide for electromagnetic safety: the stress response, *Bioelectromagnetics* 25 (2004) 642–646, discussion 647–648.
- [155] E. Padmini, Physiological adaptations of stressed fish to polluted environments: role of heat shock proteins, *Rev. Environ. Contam. Toxicol.* 206 (2010) 1–27.
- [156] P. Bottoni, B. Giardina, R. Scatena, Proteomic profiling of heat shock proteins: an emerging molecular approach with direct pathophysiological and clinical implications, *Proteomics. Clin. Appl.* 3 (2009) 636–653.
- [157] I. George, M.S. Geddis, Z. Lill, H. Lin, T. Gomez, M. Blank, M.C. Oz, R. Goodman, Myocardial function improved by electromagnetic field induction of stress protein hsp70, *J. Cell. Physiol.* 216 (2008) 816–823.
- [158] H. Bohr, J. Bohr, Microwave enhanced kinetics observed in ORD studies of a protein, *Bioelectromagnetics* 21 (2000) 68–72.
- [159] F. Mancinelli, M. Caraglia, A. Abbruzzese, G. d'Ambrosio, R. Massa, E. Bismuto, Non-thermal effects of electromagnetic fields at mobile phone frequency on the refolding of an intracellular protein: myoglobin, *J. Cell. Biochem.* 93 (2004) 188–196.
- [160] A. El-Ansary, L. Al-Ayadi, Neuroinflammation in autism spectrum disorders, *J. Neuroinflamm.* 9 (2012) 265.
- [161] M. Evers, C. Cunningham-Rundles, E. Hollander, Heat shock protein 90 antibodies in autism, *Mol. Psychiatry* 7 (Suppl. 2) (2002) S26–S28.



- [162] A.K. El-Ansary, A. Ben Bacha, M. Kotb, Etiology of autistic features: the persisting neurotoxic effects of propionic acid, *J. Neuroinflamm.* 9 (2012) 74.
- [163] S.J. Walker, J. Segal, M. Aschner, Cultured lymphocytes from autistic children and non-autistic siblings up-regulate heat shock protein RNA in response to thimerosal challenge, *Neurotoxicology* 27 (2006) 685–692.
- [164] A. Vojdani, M. Bazargan, E. Vojdani, J. Samadi, A.A. Nourian, N. Eghbalieh, E.L. Cooper, Heat shock protein and gliadin peptide promote development of peptidase antibodies in children with autism and patients with autoimmune disease, *Clin. Diagn. Lab. Immunol.* 11 (2004) 515–524.
- [165] G.D. Mironova, M. Baumann, O. Kolomytkin, Z. Krasichkova, A. Berdimuratov, T. Sirota, I. Virtanen, N.E. Saris, Purification of the channel component of the mitochondrial calcium uniporter and its reconstitution into planar lipid bilayers, *J. Bioenerg. Biomembr.* 26 (1994) 231–238.
- [166] R. Liburdy, Cellular studies and interaction mechanisms of extremely low frequency fields, *Radio Sci.* 20 (1995) 179–203.
- [167] M. Ishido, H. Nitta, M. Kabuto, Magnetic fields (MF) of 50 Hz at 1.2 microT as well as 100 microT cause uncoupling of inhibitory pathways of adenylyl cyclase mediated by melatonin 1a receptor in MF-sensitive MCF-7 cells, *Carcinogenesis* 22 (2001) 1043–1048.
- [168] C.V. Byus, S.E. Pieper, W.R. Adey, The effects of low-energy 60-Hz environmental electromagnetic fields upon the growth-related enzyme ornithine decarboxylase, *Carcinogenesis* 8 (1987) 1385–1389.
- [169] G. Chen, B.L. Upham, W. Sun, C.C. Chang, E.J. Rothwell, K.M. Chen, H. Yamasaki, J.E. Trosko, Effect of electromagnetic field exposure on chemically induced differentiation of friend erythroleukemia cells, *Environ. Health Perspect.* 108 (2000) 967–972.
- [170] T.A. Litovitz, D. Krause, M. Penafiel, E.C. Elson, J.M. Mullins, The role of coherence time in the effect of microwaves on ornithine decarboxylase activity, *Bioelectromagnetics* 14 (1993) 395–403.
- [171] L.M. Penafiel, T. Litovitz, D. Krause, A. Desta, J.M. Mullins, Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells, *Bioelectromagnetics* 18 (1997) 132–141.
- [172] C.D. Cain, D.L. Thomas, W.R. Adey, 60 Hz magnetic field acts as co-promoter in focus formation of C3H/10T1/2 cells, *Carcinogenesis* 14 (1993) 955–960.
- [173] M. Mevissen, M. Haussler, W. Loscher, Alterations in ornithine decarboxylase activity in the rat mammary gland after different periods of 50 Hz magnetic field exposure, *Bioelectromagnetics* 20 (1999) 338–346.
- [174] W.R. Adey, Evidence for nonthermal electromagnetic bioeffects: potential health risks in evolving low-frequency & microwave environments, *R. College Phys. Lond.* 2002 (May) (2002) 16–17.
- [175] N.R. Desai, K.K. Kesari, A. Agarwal, Pathophysiology of cell phone radiation: oxidative stress and carcinogenesis with focus on male reproductive system, *Reprod. Biol. Endocrinol.* 7 (2009) 114.
- [176] A.M. Phelan, D.G. Lange, H.A. Kues, G.A. Luty, Modification of membrane fluidity in melanin-containing cells by low-level microwave radiation, *Bioelectromagnetics* 13 (1992) 131–146.
- [177] A. Beneduci, L. Filippelli, K. Cosentino, M.L. Calabrese, R. Massa, G. Chidichimo, Microwave induced shift of the main phase transition in phosphatidylcholine membranes, *Bioelectrochemistry* 84 (2012) 18–24.
- [178] K.W. Linz, C. von Westphalen, J. Streckert, V. Hansen, R. Meyer, Membrane potential and currents of isolated heart muscle cells exposed to pulsed radio frequency fields, *Bioelectromagnetics* 20 (1999) 497–511.
- [179] M.C. Cammaerts, O. Debeir, R. Cammaerts, Changes in *Paramecium caudatum* (protozoa) near a switched-on GSM telephone, *Electromagn. Biol. Med.* 30 (2011) 57–66.
- [180] A. El-Ansary, S. Al-Daihan, A. Al-Dbass, L. Al-Adadhi, Measurement of selected ions related to oxidative stress and energy metabolism in Saudi autistic children, *Clin. Biochem.* 43 (2010) 63–70.
- [181] Y. Zhang, Y. Sun, F. Wang, Z. Wang, Y. Peng, R. Li, Downregulating the canonical Wnt/beta-catenin signaling pathway attenuates the susceptibility to autism-like phenotypes by decreasing oxidative stress, *Neurochem. Res.* 37 (2012) 1409–1419.
- [182] Y. Al-Gadani, A. El-Ansary, O. Attas, L. Al-Adadhi, Metabolic biomarkers related to oxidative stress and antioxidant status in Saudi autistic children, *Clin. Biochem.* 42 (2009) 1032–1040.
- [183] X. Ming, T.P. Stein, M. Brimacombe, W.G. Johnson, G.H. Lambert, G.C. Wagner, Increased excretion of a lipid peroxidation biomarker in autism, *Prostaglandins Leukot. Essent. Fatty Acids* 73 (2005) 379–384.
- [184] S.S. Zoroglu, F. Armutcu, S. Ozen, A. Gurel, E. Sivasli, O. Yetkin, I. Meram, Increased oxidative stress and altered activities of erythrocyte free radical scavenging enzymes in autism, *Eur. Arch. Psychiatry Clin. Neurosci.* 254 (2004) 143–147.
- [185] M.L. Pall, Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects, *J. Cell. Mol. Med.* 17 (2013) 958–965.
- [186] V. Nesin, A.M. Bowman, S. Xiao, A.G. Pakhomov, Cell permeabilization and inhibition of voltage-gated Ca(2+) and Na(+) channel currents by nanosecond pulsed electric field, *Bioelectromagnetics* 33 (2012) 394–404.
- [187] D. Maskey, H.J. Kim, H.G. Kim, M.J. Kim, Calcium-binding proteins and GFAP immunoreactivity alterations in murine hippocampus after 1 month of exposure to 835 MHz radiofrequency at SAR values of 1.6 and 4.0 W/kg, *Neurosci. Lett.* 506 (2012) 292–296.
- [188] D. Maskey, M. Kim, B. Aryal, J. Pradhan, I.Y. Choi, K.S. Park, T. Son, S.Y. Hong, S.B. Kim, H.G. Kim, M.J. Kim, Effect of 835 MHz radiofrequency radiation exposure on calcium binding proteins in the hippocampus of the mouse brain, *Brain Res.* 1313 (2010) 232–241.
- [189] A. Kittel, L. Siklos, G. Thuroczy, Z. Somosy, Qualitative enzyme histochemistry and microanalysis reveals changes in ultrastructural distribution of calcium and calcium-activated ATPases after microwave irradiation of the medial habenula, *Acta Neuropathol.* 92 (1996) 362–368.
- [190] S.M. Bawin, W.R. Adey, Sensitivity of calcium binding in cerebral tissue to weak environmental electric fields oscillating at low frequency, *Proc. Natl. Acad. Sci. U. S. A.* 73 (1976) 1999–2003.
- [191] C.F. Blackman, S.G. Benane, D.E. House, W.T. Joines, Effects of ELF (1–120 Hz) and modulated (50 Hz) RF fields on the efflux of calcium ions from brain tissue in vitro, *Bioelectromagnetics* 6 (1985) 1–11.
- [192] C. Blackman, Induction of calcium efflux from brain tissue by radio frequency radiation, *Radio Sci.* 14 (1979) 93–98.
- [193] S.K. Dutta, B. Ghosh, C.F. Blackman, Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture, *Bioelectromagnetics* 10 (1989) 197–202.
- [194] S. Lin-Liu, W.R. Adey, Low frequency amplitude modulated microwave fields change calcium efflux rates from synaptosomes, *Bioelectromagnetics* 3 (1982) 309–322.
- [195] C.V. Byus, K. Kartun, S. Pieper, W.R. Adey, Increased ornithine decarboxylase activity in cultured cells exposed to low energy modulated microwave fields and phorbol ester tumor promoters, *Cancer Res.* 48 (1988) 4222–4226.
- [196] W. Adey, A growing scientific consensus on the cell and molecular biology mediating interactions with EM fields, in: *Symposium on Electromagnetic Transmissions, Health Hazards, Scientific Evidence and Recent Steps in Mitigation*, 1994.
- [197] S.K. Dutta, K. Das, B. Ghosh, C.F. Blackman, Dose dependence of acetylcholinesterase activity in neuroblastoma cells exposed to modulated radio-frequency electromagnetic radiation, *Bioelectromagnetics* 13 (1992) 317–322.
- [198] M. Smith, P.L. Flodman, J.J. Gargus, M.T. Simon, K. Verrell, R. Haas, G.E. Reiner, R. Naviaux, K. Osann, M.A. Spence, D.C. Wallace, Mitochondrial and ion channel gene alterations in autism, *Biochim. Biophys. Acta* 1817 (2012) 1796–1802.

- [199] J.F. Krey, R.E. Dolmetsch, Molecular mechanisms of autism: a possible role for  $\text{Ca}^{2+}$  signaling, *Curr. Opin. Neurobiol.* 17 (2007) 112–119.
- [200] S.P. Pasca, T. Portmann, I. Voineagu, M. Yazawa, A. Shcheglovitov, A.M. Pasca, B. Cord, T.D. Palmer, S. Chikahisa, S. Nishino, J.A. Bernstein, J. Hallmayer, D.H. Geschwind, R.E. Dolmetsch, Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome, *Nat. Med.* 17 (2011) 1657–1662.
- [201] J.J. Gargus, Mitochondrial component of calcium signaling abnormality in autism, in: A. Chauhan, V. Chauhan, T. Brown (Eds.), *Autism: Oxidative Stress, Inflammation and Immune Abnormalities*, CRC Press, Boca Raton, FL, 2009, pp. 207–224.
- [202] A.T. Lu, X. Dai, J.A. Martinez-Agosto, R.M. Cantor, Support for calcium channel gene defects in autism spectrum disorders, *Mol. Autism* 3 (2012) 18.
- [203] L. Palmieri, A.M. Persico, Mitochondrial dysfunction in autism spectrum disorders: cause or effect? *Biochim. Biophys. Acta* 1797 (2010) 1130–1137.
- [204] T.I. Peng, M.J. Jou, Oxidative stress caused by mitochondrial calcium overload, *Ann. N. Y. Acad. Sci.* 1201 (2010) 183–188.
- [205] I.N. Pessah, P.J. Lein, Evidence for Environmental Susceptibility in Autism: What We Need to Know About Gene  $\times$  Environment Interactions, *Humana*, 2008.
- [206] G.A. Wayman, D.D. Bose, D. Yang, A. Lesiak, D. Bruun, S. Impey, V. Ledoux, I.N. Pessah, P.J. Lein, PCB-95 modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth, *Environ. Health Perspect.* 120 (2012) 1003–1009.
- [207] G.A. Wayman, D. Yang, D.D. Bose, A. Lesiak, V. Ledoux, D. Bruun, I.N. Pessah, P.J. Lein, PCB-95 promotes dendritic growth via ryanodine receptor-dependent mechanisms, *Environ. Health Perspect.* 120 (2012) 997–1002.
- [208] M. Stamou, K.M. Streifel, P.E. Goines, P.J. Lein, Neuronal connectivity as a convergent target of gene-environment interactions that confer risk for autism spectrum disorders, *Neurotoxicol. Teratol.* 36 (2013) 3–16.
- [209] F. Cervellati, G. Franceschetti, L. Lunghi, S. Franzellitti, P. Valbonesi, E. Fabbri, C. Biondi, F. Vesce, Effect of high-frequency electromagnetic fields on trophoblastic connexins, *Reprod. Toxicol.* 28 (2009) 59–65.
- [210] Z. Palfia, Z. Somosy, G. Rez, Tight junctional changes upon microwave and X-ray irradiation, *Acta Biol. Hung.* 52 (2001) 411–416.
- [211] S.H. Fatemi, T.D. Folsom, T.J. Reutiman, S. Lee, Expression of astrocytic markers aquaporin 4 and connexin 43 is altered in brains of subjects with autism, *Synapse* 62 (2008) 501–507.
- [212] R.H. Thomas, M.M. Meeking, J.R. Mephram, L. Tichenoff, F. Possmayer, S. Liu, D.F. MacFabe, The enteric bacterial metabolite propionic acid alters brain and plasma phospholipid molecular species: further development of a rodent model of autism spectrum disorders, *J. Neuroinflamm.* 9 (2012) 153.
- [213] C.E. Onore, C.W. Nordahl, G.S. Young, J.A. Van de Water, S.J. Rogers, P. Ashwood, Levels of soluble platelet endothelial cell adhesion molecule-1 and p-selectin are decreased in children with autism spectrum disorder, *Biol. Psychiatry* 72 (2012) 1020–1025.
- [214] L.G. Salford, H. Nittby, B.R. Persson, Effects of EMF from wireless communication upon the blood–brain barrier, in: C. Sage (Ed.), *BioInitiative 2012: A Rationale for a Biologically-Based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012.
- [215] Z. Somosy, G. Thuroczy, J. Kovacs, Effects of modulated and continuous microwave irradiation on pyroantimonate precipitable calcium content in junctional complex of mouse small intestine, *Scanning Microsc.* 7 (1993) 1255–1261.
- [216] L.G. Salford, A. Brun, K. Stureson, J.L. Eberhardt, B.R. Persson, Permeability of the blood–brain barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50, and 200 Hz, *Microsc. Res. Tech.* 27 (1994) 535–542.
- [217] L.G. Salford, A.E. Brun, J.L. Eberhardt, L. Malmgren, B.R. Persson, Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones, *Environ. Health Perspect.* 111 (2003) 881–883, discussion A408.
- [218] L.G. Salford, A. Brun, G. Grafstrom, J. Eberhardt, L. Malmgren, B. Persson, Non-thermal effects of EMF upon the mammalian brain: the Lund experience, *Environmentalist* (2007) 493–500.
- [219] L.G. Salford, J. Eberhardt, L. Malmgren, B. Persson, Electromagnetic field-induced permeability of the blood–brain barrier shown by immunohistochemical methods, in: *Interaction Mechanism of Low-Level Electromagnetic Fields, Living Systems*, Oxford University Press, Oxford, 1992, pp. 251–258.
- [220] J.L. Eberhardt, B.R. Persson, A.E. Brun, L.G. Salford, L.O. Malmgren, Blood–brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones, *Electromagn. Biol. Med.* 27 (2008) 215–229.
- [221] H. Nittby, A. Brun, J. Eberhardt, L. Malmgren, B.R. Persson, L.G. Salford, Increased blood–brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone, *Pathophysiology* 16 (2009) 103–112.
- [222] H. Nittby, G. Grafstrom, J.L. Eberhardt, L. Malmgren, A. Brun, B.R. Persson, L.G. Salford, Radiofrequency and extremely low-frequency electromagnetic field effects on the blood–brain barrier, *Electromagn. Biol. Med.* 27 (2008) 103–126.
- [223] D.G. Lange, M.E. D'Antuono, R.R. Timm, T.K. Ishii, J.M. Fujimoto, Differential response of the permeability of the rat liver canalicular membrane to sucrose and mannitol following in vivo acute single and multiple exposures to microwave radiation (2.45 GHz) and radiant-energy thermal stress, *Radiat. Res.* 134 (1993) 54–62.
- [224] H.A. Kues, J.C. Monahan, S.A. D'Anna, D.S. McLeod, G.A. Lutty, S. Koslov, Increased sensitivity of the non-human primate eye to microwave radiation following ophthalmic drug pretreatment, *Bioelectromagnetics* 13 (1992) 379–393.
- [225] S.R. Parathath, S. Parathath, S.E. Tsirka, Nitric oxide mediates neurodegeneration and breakdown of the blood–brain barrier in tPA-dependent excitotoxic injury in mice, *J. Cell Sci.* 119 (2006) 339–349.
- [226] B. Hassel, E.G. Iversen, F. Fonnum, Neurotoxicity of albumin in vivo, *Neurosci. Lett.* 167 (1994) 29–32.
- [227] S. Eimerl, M. Schramm, Acute glutamate toxicity and its potentiation by serum albumin are determined by the  $\text{Ca}^{2+}$  concentration, *Neurosci. Lett.* 130 (1991) 125–127.
- [228] B.V. Zlokovic, The blood–brain barrier in health and chronic neurodegenerative disorders, *Neuron* 57 (2008) 178–201.
- [229] M. Boso, E. Emanuele, P. Minorette, M. Arra, P. Politi, S. Ucelli di Nemi, F. Barale, Alterations of circulating endogenous secretory RAGE and S100A9 levels indicating dysfunction of the AGE-RAGE axis in autism, *Neurosci. Lett.* 410 (2006) 169–173.
- [230] A.M. Young, E. Campbell, S. Lynch, J. Suckling, S.J. Powis, Aberrant NF-kappaB expression in autism spectrum condition: a mechanism for neuroinflammation, *Front. Psychiatry* 2 (2011) 27.
- [231] M.A. Erickson, K. Dohi, W.A. Banks, Neuroinflammation: a common pathway in CNS diseases as mediated at the blood–brain barrier, *Neuroimmunomodulation* 19 (2012) 121–130.
- [232] D. Janigro, Are you in or out? Leukocyte, ion, and neurotransmitter permeability across the epileptic blood–brain barrier, *Epilepsia* 53 (Suppl. 1) (2012) 26–34.
- [233] Y. Takeshita, R.M. Ransohoff, Inflammatory cell trafficking across the blood–brain barrier: chemokine regulation and in vitro models, *Immunol. Rev.* 248 (2012) 228–239.
- [234] N. Boddaert, M. Zilbovicius, A. Philipe, L. Robel, M. Bourgeois, C. Barthelemy, D. Seidenwurm, I. Meresse, L. Laurier, I. Desguerre, N. Bahi-Buisson, F. Brunelle, A. Munnich, Y. Samson, M.C. Mouren, N. Chabane, MRI findings in 77 children with non-syndromic autistic disorder, *PLoS ONE* 4 (2009) e4415.
- [235] N. Vardi, N. Freedman, H. Lester, J.M. Gomori, R. Chisin, B. Lerer, O. Bonne, Hyperintensities on T2-weighted images in the basal



- ganglia of patients with major depression: cerebral perfusion and clinical implications, *Psychiatry Res.* 192 (2011) 125–130.
- [236] A.M. Brickman, J. Muraskin, M.E. Zimmerman, Structural neuroimaging in Alzheimer's disease: do white matter hyperintensities matter? *Dialogues Clin. Neurosci.* 11 (2009) 181–190.
- [237] L. de Magistris, V. Familiari, A. Pascotto, A. Sapone, A. Froli, P. Iardino, M. Carteni, M. De Rosa, R. Francavilla, G. Riegler, R. Militerni, C. Bravaccio, Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives, *J. Pediatr. Gastroenterol. Nutr.* 51 (2010) 418–424.
- [238] S. Lucarelli, T. Frediani, A.M. Zingoni, F. Ferruzzi, O. Giardini, F. Quintieri, M. Barbato, P. D'Eufemia, E. Cardi, Food allergy and infantile autism, *Panminerva Med.* 37 (1995) 137–141.
- [239] P. D'Eufemia, M. Celli, R. Finocchiario, L. Pacifico, L. Viozzi, M. Zaccagnini, E. Cardi, O. Giardini, Abnormal intestinal permeability in children with autism, *Acta Paediatr.* 85 (1996) 1076–1079.
- [240] K. Horvath, J.A. Perman, Autism and gastrointestinal symptoms, *Curr. Gastroenterol. Rep.* 4 (2002) 251–258.
- [241] J.F. White, Intestinal pathophysiology in autism, *Exp. Biol. Med.* (Maywood) 228 (2003) 639–649.
- [242] M.A. Robertson, D.L. Sigalet, J.J. Holst, J.B. Meddings, J. Wood, K.A. Sharkey, Intestinal permeability and glucagon-like peptide-2 in children with autism: a controlled pilot study, *J. Autism Dev. Disord.* 38 (2008) 1066–1071.
- [243] N.C. Souza, J.N. Mendonca, G.V. Portari, A.A. Jordao Junior, J.S. Marchini, P.G. Chiarello, Intestinal permeability and nutritional status in developmental disorders, *Altern. Ther. Health Med.* 18 (2012) 19–24.
- [244] M.A. Silva, J. Jury, Y. Sanz, M. Wiepjes, X. Huang, J.A. Murray, C.S. David, A. Fasano, E.F. Verdu, Increased bacterial translocation in gluten-sensitive mice is independent of small intestinal paracellular permeability defect, *Dig. Dis. Sci.* 57 (2012) 38–47.
- [245] A. Sapone, K.M. Lammers, V. Casolaro, M. Cammarota, M.T. Giuliano, M. De Rosa, R. Stefanile, G. Mazzarella, C. Tolone, M.I. Russo, P. Esposito, F. Ferraraccio, M. Carteni, G. Riegler, L. de Magistris, A. Fasano, Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity, *BMC Med.* 9 (2011) 23.
- [246] J. Visser, J. Rozing, A. Sapone, K. Lammers, A. Fasano, Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms, *Ann. N. Y. Acad. Sci.* 1165 (2009) 195–205.
- [247] M. Simpson, M. Mojibian, K. Barriga, F.W. Scott, A. Fasano, M. Rewers, J.M. Norris, An exploration of GLO-3A antibody levels in children at increased risk for type 1 diabetes mellitus, *Pediatr. Diabetes* 10 (2009) 563–572.
- [248] A. Fasano, Surprises from celiac disease, *Sci. Am.* 301 (2009) 54–61.
- [249] K.M. Lammers, R. Lu, J. Brownley, B. Lu, C. Gerard, K. Thomas, P. Rallabhandi, T. Shea-Donohue, A. Tamiz, S. Alkan, S. Netzel-Arnett, T. Antal, S.N. Vogel, A. Fasano, Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3, *Gastroenterology* 135 (2008) 194–204, e193.
- [250] M. De Angelis, C.G. Rizzello, A. Fasano, M.G. Clemente, C. De Simone, M. Silano, M. De Vincenzi, I. Losito, M. Gobetti, VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for Celiac Sprue, *Biochim. Biophys. Acta* 1762 (2006) 80–93.
- [251] T.C. Theoharides, R. Doyle, Autism, gut-blood-brain barrier, and mast cells, *J. Clin. Psychopharmacol.* 28 (2008) 479–483.
- [252] E.Y. Hsiao, P.H. Patterson, Placental regulation of maternal-fetal interactions and brain development, *Dev. Neurobiol.* 72 (2012) 1317–1326.
- [253] M. Herbert, Autism: from static genetic brain defect to dynamic gene-environment modulated pathophysiology, in: S. Krimsky, J. Gruber (Eds.), *Genetic Explanations: Sense and Nonsense*, Harvard University Press, Cambridge, MA, 2013, pp. 122–146.
- [254] M. King, P. Bearman, Diagnostic change and the increased prevalence of autism, *Int. J. Epidemiol.* 38 (2009) 1224–1234.
- [255] I. Hertz-Picciotto, L. Delwiche, The rise in autism and the role of age at diagnosis, *Epidemiology* 20 (2009) 84–90.
- [256] R. Anney, L. Klei, D. Pinto, R. Regan, J. Conroy, T.R. Magalhaes, C. Correia, B.S. Abrahams, N. Sykes, A.T. Pagnamenta, J. Almeida, E. Bacchelli, A.J. Bailey, G. Baird, A. Battaglia, T. Berney, N. Bolshakova, S. Bolte, P.F. Bolton, T. Bourgeron, S. Brennan, J. Brian, A.R. Carson, G. Casallo, J. Casey, S.H. Chu, L. Cochrane, C. Corsello, E.L. Crawford, A. Crossett, G. Dawson, M. de Jonge, R. Delorme, I. Drmic, E. Duketis, F. Duque, A. Estes, P. Farrar, B.A. Fernandez, S.E. Folstein, E. Fombonne, C.M. Freitag, J. Gilbert, C. Gillberg, J.T. Glessner, J. Goldberg, J. Green, S.J. Guter, H. Hakonarson, E.A. Heron, M. Hill, R. Holt, J.L. Howe, G. Hughes, V. Hus, R. Iglizzi, C. Kim, S.M. Klauck, A. Kolevzon, O. Korvatska, V. Kustanovich, C.M. Lajonchere, J.A. Lamb, M. Laskawiec, M. Leboyer, A. Le Couteur, B.L. Leventhal, A.C. Lionel, X.Q. Liu, C. Lord, L. Lotspeich, S.C. Lund, E. Maestrini, W. Mahoney, C. Mantoulan, C.R. Marshall, H. McConachie, C.J. McDougle, J. McGrath, W.M. McMahon, N.M. Melhem, A. Merikangas, O. Migita, N.J. Minshew, G.K. Mirza, J. Munson, S.F. Nelson, C. Noakes, A. Noor, G. Nygren, G. Oliveira, K. Papanikolaou, J.R. Parr, B. Parrini, T. Paton, A. Pickles, J. Piven, D.J. Posey, A. Poustka, F. Poustka, A. Prasad, J. Ragoussis, K. Renshaw, J. Rickaby, W. Roberts, K. Roeder, B. Røge, M.L. Rutter, L.J. Bierut, J.P. Rice, J. Salt, K. Sansom, D. Sato, R. Segurado, L. Senman, N. Shah, V.C. Sheffield, L. Soorya, I. Sousa, V. Stoppioni, C. Strawbridge, R. Tancredi, K. Tansey, B. Thiruvahindrapuram, A.P. Thompson, S. Thomson, A. Tryfon, J. Tziantis, H. Van Engeland, J.B. Vincent, F. Volkmar, S. Wallace, K. Wang, Z. Wang, T.H. Wassink, K. Wing, K. Wittmeyer, S. Wood, B.L. Yaspan, D. Zurawiecki, L. Zwaigenbaum, C. Betancur, J.D. Buxbaum, R.M. Cantor, E.H. Cook, H. Coon, M.L. Cuccaro, L. Gallagher, D.H. Geschwind, M. Gill, J.L. Haines, J. Miller, A.P. Monaco, J.I. Nurnberger Jr., A.D. Paterson, M.A. Pericak-Vance, G.D. Schellenberg, S.W. Scherer, J.S. Sutcliffe, P. Szatmari, A.M. Vicente, V.J. Vieland, E.M. Wijsman, B. Devlin, S. Ennis, J. Hallmayer, A genome-wide scan for common alleles affecting risk for autism, *Hum. Mol. Genet.* 19 (2010) 4072–4082.
- [257] C. Betancur, Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting, *Brain Res.* 1380 (2011) 42–77.
- [258] J. Hallmayer, S. Cleveland, A. Torres, J. Phillips, B. Cohen, T. Torigoe, J. Miller, A. Fedele, J. Collins, K. Smith, L. Lotspeich, L.A. Croen, S. Ozonoff, C. Lajonchere, J.K. Grether, N. Risch, Genetic heritability and shared environmental factors among twin pairs with autism, *Arch. Gen. Psychiatry* 68 (2011) 1095–1102.
- [259] J.O. Davis, J.A. Phelps, H.S. Bracha, Prenatal development of monozygotic twins and concordance for schizophrenia, *Schizophr. Bull.* 21 (1995) 357–366.
- [260] D.K. Kinney, D.H. Barch, B. Chayka, S. Napoleon, K.M. Munir, Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder? *Med. Hypotheses* 74 (2010) 102–106.
- [261] H.W. Ruediger, Genotoxic effects of radiofrequency electromagnetic fields, *Pathophysiology* 16 (2009) 89–102.
- [262] S. Ivancsits, A. Pilger, E. Diem, O. Jahn, H.W. Rudiger, Cell type-specific genotoxic effects of intermittent extremely low-frequency electromagnetic fields, *Mutat. Res.* 583 (2005) 184–188.
- [263] E. Diem, C. Schwarz, F. Adlkofer, O. Jahn, H. Rudiger, Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro, *Mutat. Res.* 583 (2005) 178–183.
- [264] M. Blank, R. Goodman, DNA is a fractal antenna in electromagnetic fields, *Int. J. Radiat. Biol.* 87 (2011) 409–415.

- [265] REFLEX, Final Report, REFLEX (Risk Evaluation of Potential Environmental Hazards From Low-Energy Electromagnetic Field Exposure Using Sensitive in vitro Methods), Key Action 4 “Environment and Health”, in: Quality of Life and Management of Living Resources. European Union, 2004, 31 May, [http://ec.europa.eu/research/environment/pdf/env\\_health\\_projects/electromagnetic\\_fields/e-reflex.pdf](http://ec.europa.eu/research/environment/pdf/env_health_projects/electromagnetic_fields/e-reflex.pdf)
- [266] C. Sage, D.O. Carpenter, Public health implications of wireless technologies, *Pathophysiology* 16 (2009) 233–246.
- [267] B.M. Neale, Y. Kou, L. Liu, A. Ma'ayan, K.E. Samocha, A. Sabo, C.F. Lin, C. Stevens, L.S. Wang, V. Makarov, P. Polak, S. Yoon, J. Maguire, E.L. Crawford, N.G. Campbell, E.T. Geller, O. Valladares, C. Schafer, H. Liu, T. Zhao, G. Cai, J. Lihm, R. Dannenfelser, O. Jabado, Z. Peralta, U. Nagaswamy, D. Muzny, J.G. Reid, I. Newsham, Y. Wu, L. Lewis, Y. Han, B.F. Voight, E. Lim, E. Rossin, A. Kirby, J. Flannick, M. Fromer, K. Shakir, T. Fennell, K. Garimella, E. Banks, R. Poplin, S. Gabriel, M. DePristo, J.R. Wimbish, B.E. Boone, S.E. Levy, C. Betancur, S. Sunyaev, E. Boerwinkle, J.D. Buxbaum, E.H. Cook Jr., B. Devlin, R.A. Gibbs, K. Roeder, G.D. Schellenberg, J.S. Sutcliffe, M.J. Daly, Patterns and rates of exonic de novo mutations in autism spectrum disorders, *Nature* 485 (2012) 242–245.
- [268] B.J. O’Roak, L. Vives, S. Girirajan, E. Karakoc, N. Krumm, B.P. Coe, R. Levy, A. Ko, C. Lee, J.D. Smith, E.H. Turner, I.B. Stanaway, B. Vernot, M. Malig, C. Baker, B. Reilly, J.M. Akey, E. Borenstein, M.J. Rieder, D.A. Nickerson, R. Bernier, J. Shendure, E.E. Eichler, Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations, *Nature* 485 (2012) 246–250.
- [269] S.J. Sanders, M.T. Murtha, A.R. Gupta, J.D. Murdoch, M.J. Raubeson, A.J. Willsey, A.G. Ercan-Sencicek, N.M. DiLullo, N.N. Parikshak, J.L. Stein, M.F. Walker, G.T. Ober, N.A. Teran, Y. Song, P. El-Fishawy, R.C. Murtha, M. Choi, J.D. Overton, R.D. Bjornson, N.J. Carriero, K.A. Meyer, K. Bilguvar, S.M. Mane, N. Sestan, R.P. Lifton, M. Gunel, K. Roeder, D.H. Geschwind, B. Devlin, M.W. State, De novo mutations revealed by whole-exome sequencing are strongly associated with autism, *Nature* 485 (2012) 237–241.
- [270] E. Markova, L. Hillert, L. Malmgren, B.R. Persson, I.Y. Belyaev, Microwaves from GSM mobile telephones affect 53BP1 and gamma-H2AX foci in human lymphocytes from hypersensitive and healthy persons, *Environ. Health Perspect.* 113 (2005) 1172–1177.
- [271] I.Y. Belyaev, L. Hillert, M. Protopopova, C. Tamm, L.O. Malmgren, B.R. Persson, G. Selivanova, M. Harms-Ringdahl, 915 MHz microwaves and 50 Hz magnetic field affect chromatin conformation and 53BP1 foci in human lymphocytes from hypersensitive and healthy persons, *Bioelectromagnetics* 26 (2005) 173–184.
- [272] E. Markova, L.O.G. Malmgren, I. Belyaev, Microwaves from mobile phones inhibit 53BP1 focus formation in human stem cells more strongly than in differentiated cells: possible mechanistic link to cancer risk, *Environ. Health Perspect.* (2010) 394–399.
- [273] O.A. Christophersen, A. Haug, Animal products, diseases and drugs: a plea for better integration between agricultural sciences, human nutrition and human pharmacology, *Lipids Health Dis.* 10 (2011) 16.
- [274] I. Belyaev, Y.D. Alipov, M. Harms-Ringdahl, Effects of zero magnetic field on the conformation of chromatin in human cells, *Biochim. Biophys. Acta* 1336 (1997) 465–473.
- [275] S. Belyaev, V. Kravchenko, Resonance effect of low-intensity millimeter waves on the chromatin conformational state of rat thymocytes, *Z. Naturforsch.* 49 (1994).
- [276] C. Paul, M. Nagano, B. Robaire, Aging results in differential regulation of DNA repair pathways in pachytene spermatocytes in the Brown Norway rat, *Biol. Reprod.* 85 (2011) 1269–1278.
- [277] I. Iossifov, M. Ronemus, D. Levy, Z. Wang, I. Hakker, J. Rosenbaum, B. Yamrom, Y.H. Lee, G. Narzisi, A. Leotta, J. Kendall, E. Grabowska, B. Ma, S. Marks, L. Rodgers, A. Stepansky, J. Troge, P. Andrews, M. Bekritsky, K. Pradhan, E. Ghiban, M. Kramer, J. Parla, R. Demeter, L.L. Fulton, R.S. Fulton, V.J. Magrini, K. Ye, J.C. Darnell, R.B. Darnell, E.R. Mardis, R.K. Wilson, M.C. Schatz, W.R. McCombie, M. Wigler, De novo gene disruptions in children on the autistic spectrum, *Neuron* 74 (2012) 285–299.
- [278] R.M. Cantor, J.L. Yoon, J. Furr, C.M. Lajonchere, Paternal age and autism are associated in a family-based sample, *Mol. Psychiatry* 12 (2007) 419–421.
- [279] M.D. Alter, R. Kharkar, K.E. Ramsey, D.W. Craig, R.D. Melmed, T.A. Grebe, R.C. Bay, S. Ober-Reynolds, J. Kirwan, J.J. Jones, J.B. Turner, R. Hen, D.A. Stephan, Autism and increased paternal age related changes in global levels of gene expression regulation, *PLoS ONE* 6 (2011) e16715.
- [280] A. Agarwal, F. Deepinder, R.K. Sharma, G. Ranga, J. Li, Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study, *Fertil. Steril.* 89 (2008) 124–128.
- [281] A. Agarwal, N.R. Desai, K. Makker, A. Varghese, R. Mouradi, E. Sabanegh, R. Sharma, Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study, *Fertil. Steril.* 92 (2009) 1318–1325.
- [282] A. Wdowiak, L. Wdowiak, H. Wiktor, Evaluation of the effect of using mobile phones on male fertility, *Ann. Agric. Environ. Med.* 14 (2007) 169–172.
- [283] I. Fejes, Z. Zavaczki, J. Szollosi, S. Koloszar, J. Daru, L. Kovacs, A. Pal, Is there a relationship between cell phone use and semen quality? *Arch. Androl.* 51 (2005) 385–393.
- [284] R.J. Aitken, L.E. Bennetts, D. Sawyer, A.M. Wiklendt, B.V. King, Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline, *Int. J. Androl.* 28 (2005) 171–179.
- [285] O. Erogul, E. Oztas, I. Yildirim, T. Kir, E. Aydur, G. Komesli, H.C. Irkilata, M.K. Irmak, A.F. Peker, Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study, *Arch. Med. Res.* 37 (2006) 840–843.
- [286] S. Dasdag, M.A. Ketani, Z. Akdag, A.R. Ersay, I. Sari, O.C. Demirtas, M.S. Celik, Whole-body microwave exposure emitted by cellular phones and testicular function of rats, *Urol. Res.* 27 (1999) 219–223.
- [287] J.G. Yan, M. Agresti, T. Bruce, Y.H. Yan, A. Granlund, H.S. Matloub, Effects of cellular phone emissions on sperm motility in rats, *Fertil. Steril.* 88 (2007) 957–964.
- [288] A.A. Otitoloju, I.A. Obe, O.A. Adewale, O.A. Otubanjo, V.O. Osunkalu, Preliminary study on the induction of sperm head abnormalities in mice, *Mus musculus*, exposed to radiofrequency radiations from global system for mobile communication base stations, *Bull. Environ. Contam. Toxicol.* 84 (2010) 51–54.
- [289] N. Salama, T. Kishimoto, H.O. Kanayama, S. Kagawa, The mobile phone decreases fructose but not citrate in rabbit semen: a longitudinal study, *Syst. Biol. Reprod. Med.* 55 (2009) 181–187.
- [290] K.K. Kesari, S. Kumar, J. Nirala, M.H. Siddiqui, J. Behari, Biophysical evaluation of radiofrequency electromagnetic field effects on male reproductive pattern, *Cell Biochem. Biophys.* 65 (2013) 85–96.
- [291] A.A. Zalata, A.B. Christophe, C.E. Depuydt, F. Schoonjans, F.H. Comhaire, The fatty acid composition of phospholipids of spermatozoa from infertile patients, *Mol. Hum. Reprod.* 4 (1998) 111–118.
- [292] A. Zalata, T. Hafez, F. Comhaire, Evaluation of the role of reactive oxygen species in male infertility, *Hum. Reprod.* 10 (1995) 1444–1451.
- [293] D.J. Panagopoulos, Effect of microwave exposure on the ovarian development of *Drosophila melanogaster*, *Cell Biochem. Biophys.* 63 (2012) 121–132.

- [294] A. Gul, H. Celebi, S. Ugras, The effects of microwave emitted by cellular phones on ovarian follicles in rats, *Arch. Gynecol. Obstet.* 280 (2009) 729–733.
- [295] I.N. Magras, T.D. Xenos, RF radiation-induced changes in the prenatal development of mice, *Bioelectromagnetics* 18 (1997) 455–461.
- [296] S. Silberman, The Geek Syndrome, *Wired*, 2001.
- [297] N.C. Derecki, J.C. Cronk, Z. Lu, E. Xu, S.B. Abbott, P.G. Guyenet, J. Kipnis, Wild-type microglia arrest pathology in a mouse model of Rett syndrome, *Nature* 484 (2012) 105–109.
- [298] N.C. Derecki, J.C. Cronk, J. Kipnis, The role of microglia in brain maintenance: implications for Rett syndrome, *Trends Immunol.* 34 (2013) 144–150.

Autism and EMF? Plausibility of a pathophysiological link.  
Pathophysiology, Part II. (Herbert et al); 2013



# Autism and EMF? Plausibility of a pathophysiological link part II

Martha R. Herbert<sup>a,\*</sup>, Cindy Sage<sup>b</sup>

<sup>a</sup> *Massachusetts General Hospital Harvard Medical School Boston, TRANSCEND Research Program Neurology, Boston, MA, USA*

<sup>b</sup> *Sage Associates, Santa Barbara, CA, USA*

## Abstract

Autism spectrum conditions (ASCs) are defined behaviorally, but they also involve multileveled disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency radiation exposures (EMF/RFR). Part I (Vol 776) of this paper reviewed the critical contributions pathophysiology may make to the etiology, pathogenesis and ongoing generation of behaviors currently defined as being core features of ASCs. We reviewed pathophysiological damage to core cellular processes that are associated both with ASCs and with biological effects of EMF/RFR exposures that contribute to chronically disrupted homeostasis. Many studies of people with ASCs have identified oxidative stress and evidence of free radical damage, cellular stress proteins, and deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASCs may be due to genetics or may be downstream of inflammation or environmental exposures. Cell membrane lipids may be peroxidized, mitochondria may be dysfunctional, and various kinds of immune system disturbances are common. Brain oxidative stress and inflammation as well as measures consistent with blood–brain barrier and brain perfusion compromise have been documented. Part II of this paper documents how behaviors in ASCs may emerge from alterations of electrophysiological oscillatory synchronization, how EMF/RFR could contribute to these by de-tuning the organism, and policy implications of these vulnerabilities. It details evidence for mitochondrial dysfunction, immune system dysregulation, neuroinflammation and brain blood flow alterations, altered electrophysiology, disruption of electromagnetic signaling, synchrony, and sensory processing, de-tuning of the brain and organism, with autistic behaviors as emergent properties emanating from this pathophysiology. Changes in brain and autonomic nervous system electrophysiological function and sensory processing predominate, seizures are common, and sleep disruption is close to universal. All of these phenomena also occur with EMF/RFR exposure that can add to system overload (‘allostatic load’) in ASCs by increasing risk, and can worsen challenging biological problems and symptoms; conversely, reducing exposure might ameliorate symptoms of ASCs by reducing obstruction of physiological repair. Various vital but vulnerable mechanisms such as calcium channels may be disrupted by environmental agents, various genes associated with autism or the interaction of both. With dramatic increases in reported ASCs that are coincident in time with the deployment of wireless technologies, we need aggressive investigation of potential ASC–EMF/RFR links. The evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels now known to be biologically disruptive, and strong, interim precautionary practices are advocated.

© 2013 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Autism; EMF/RFR; Cellular stress; Oxidative stress; Mitochondrial dysfunction; Oscillatory synchronization; Environment; Radiofrequency; Wireless; Children; Fetus; Microwave

## 1. Recap of part I and summary of part II

Part I of this two-part article previously documented a series of parallels between the pathophysiological and genotoxic impacts of EMF/RFR and the pathophysiological, genetic and environmental underpinnings of ASCs. DNA

damage, immune and blood–brain barrier disruption, cellular and oxidative stress, calcium channel dysfunction, disturbed circadian rhythms, hormone dysregulation, and degraded cognition, sleep, autonomic regulation and brainwave activity—all are associated with both ASCs and EMF/RFR; and the disruption of fertility and reproduction associated with EMF/RFR may also be related to the increasing incidence of ASCs. All of this argues for reduction of exposures now, and better coordinated research in these areas. These

\* Corresponding author.

E-mail address: [drmarthaherbert@gmail.com](mailto:drmarthaherbert@gmail.com) (M.R. Herbert).



pathophysiological parallels are laid out after identifying the dynamic features of ASCs that could plausibly arise out of such pathophysiological dysregulation. The importance of transduction between levels was also discussed in Part I.

Part II elucidates in much more detail the possible interfaces between the cellular and molecular pathophysiology reviewed above and the higher-level disruption of physiological systems, brain tissue and nervous system electrophysiology. It addresses mitochondrial dysfunction, immune system dysregulation, neuroinflammation and brain blood flow alterations, altered electrophysiology, disruption of electromagnetic signaling, synchrony, and sensory processing, de-tuning of the brain and organism, and behavior as an emergent property. The emergence of ever larger amounts of data is transforming our understanding of ASCs from static encephalopathies based on genetically caused brain damage to dynamic encephalopathies where challenging behaviors emanate from physiologically disrupted systems. In parallel, the emergence of ever larger bodies of evidence supporting a large array of non-thermal but profound pathophysiological impacts of EMF/RFR is transforming our understanding of the nature of EMF/RFR impacts on the organism. At present our policies toward ASCs are based on outdated assumptions about autism being a genetic, behavioral condition, whereas our medical, educational and public health policies related to treatment and prevention could be much more effective if we took whole-body, gene-environment considerations into account, because there are many lifestyle and environmental modifications that could reduce morbidity and probably incidence of ASCs as well. Our EMF/RFR standards are also based on an outdated assumption that it is only heating (thermal injury) which can do harm. These thermal safety limits do not address low-intensity (non-thermal) effects. The evidence is now overwhelming that limiting exposures to those causing thermal injury alone does not address the much broader array of risks and harm now clearly evident with chronic exposure to low-intensity (non-thermal) EMF/RFR. In particular, the now well-documented genotoxic impacts of EMF/RFR, placed in parallel with the huge rise in reported cases of ASCs as well as with the de novo mutations associated with some cases of ASCs (as well as other conditions), make it urgent for us to place the issue of acquired as well as inherited genetic damage on the front burner for scientific investigation and policy remediation. With the rising numbers people with ASCs and other childhood health and developmental disorders, and with the challenges to our prior assumptions posed ever more strongly by emerging evidence, we need to look for and act upon risk factors that are largely avoidable or preventable. We argue that the evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels causing biological disruption and strong, interim precautionary practices are advocated. The combined evidence in Parts I and II of this article provide substantial pathophysiological support for parallels between ASCs and EMF/RFR health impacts.

## 2. Parallels in pathophysiology

### 2.1. Degradation of the integrity of functional systems

EMF/RFR exposures can yield both psychological and physiological stress leading to chronically interrupted homeostasis. In the setting of molecular, cellular and tissue damage, one would predict that the organization and efficiency of a variety of organelles, organs and functional systems would also be degraded. In this section we will review disturbances from EMF/RFR in systems (including include oxidative and bioenergetics metabolism, immune function and electrophysiological oscillations) that include molecular and cellular components subject to the kinds of damage discussed in the previous section. We will review disturbances that have been associated with EMF/RFR, and consider the parallel disturbances that have been documented in ASCs.

#### 2.1.1. Mitochondrial dysfunction

Mitochondria are broadly vulnerable, in part because the integrity of their membranes is vital to their optimal functioning—including channels and electrical gradients, and their membranes can be damaged by free radicals which can be generated in myriad ways. Moreover, just about every step in their metabolic pathways can be targeted by environmental agents, including toxicants and drugs, as well as mutations [1]. This supports a cumulative ‘allostatic load’ model for conditions in which mitochondrial dysfunction is an issue, which includes ASCs as well as myriad other chronic conditions.

Mitochondria are commonly discussed in terms of the biochemical pathways and cascades of events by which they metabolize glucose and generate energy. But in parallel with this level of function there also appears to be a dimension of electromagnetic radiation that is part of the activity of these organelles. For example, electromagnetic radiation can be propagated through the mitochondrial reticulum, which along with the mitochondria has a higher refractive index than the surrounding cell and can serve to propagate electromagnetic radiation within the network [2]. It is also the case that “*The physiological domain is characterized by small-amplitude oscillations in mitochondrial membrane potential ( $\Delta\psi(m)$ ) showing correlated behavior over a wide range of frequencies. . . . Under metabolic stress, when the balance between ROS [reactive oxygen species, or free radicals] generation and ROS scavenging [as by antioxidants] is perturbed, the mitochondrial network throughout the cell locks to one main low-frequency, high-amplitude oscillatory mode. This behavior has major pathological implications because the energy dissipation and cellular redox changes that occur during  $\Delta\psi(m)$  depolarization result in suppression of electrical excitability and  $Ca^{2+}$  handling. . .*” [3].

These electromagnetic aspects of mitochondrial physiology and pathophysiology could very well be impacted by EMF/RFR.

Other types of mitochondrial damage have been documented in at least some of the studies that have examined the impacts of EMF/RFR upon mitochondria. These include reduced or absent mitochondrial cristae [4–6], mitochondrial DNA damage [7], swelling and crystallization [5], alterations and decreases in various lipids suggesting an increase in their use in cellular energetics [8], damage to mitochondrial DNA [7], and altered mobility and lipid peroxidation after exposures [9]. Also noted has been enhancement of brain mitochondrial function in Alzheimer's transgenic mice and normal mice [10]. The existent of positive as well as negative effects gives an indication of the high context dependence of exposure impacts, including physical factors such as frequency, duration, and tissue characteristics [11].

By now there is a large amount of evidence for biochemical and other abnormalities in a large portion of children with autism that are consistent with mitochondrial dysfunction [12–14]. Recently published postmortem brain tissue studies that have added a new dimension of evidence for mitochondrial abnormalities in ASCs will be reviewed in the section on alteration of brain cells below.

Secondary mitochondrial dysfunction (i.e. environmentally triggered rather than rooted directly in genetic mutations) [15–18] could result among other things from the already discussed potential for EMF/RFR to damage channels, membranes and mitochondria themselves as well as from toxicant exposures and immune challenges. In a meta-analysis of studies of children with ASC and mitochondrial disorder, the spectrum of severity varied, and 79% of the cases were identified by laboratory findings without associated genetic abnormalities [16].

### 2.1.2. Melatonin dysregulation

**2.1.2.1. Melatonin, mitochondria, glutathione, oxidative stress.** Melatonin is well-known for its role in regulation of circadian rhythms, but it also plays important metabolic and regulatory roles in relation to cellular protection, mitochondrial malfunction and glutathione synthesis [19–21]. It also helps prevent the breakdown of the mitochondrial membrane potential, decrease electron leakage, and thereby reduce the formation of superoxide anions [22]. Pharmacological doses of melatonin not only scavenge reactive oxygen and nitrogen species, but enhance levels of glutathione and the expression and activities of some glutathione-related enzymes [21,23].

**2.1.2.2. Melatonin can attenuate or prevent some EMF/RFR effects.** Melatonin may have a protective effect in the setting of some EMF/RFR exposures, apparently in relation to these functions just described. EMF/RFR can impact melatonin; one example is exposure to 900 MHz microwave radiation promoted oxidation, which reduced levels of melatonin and increased creatine kinase and caspase-3 in exposed as compared to sham exposed rats [24].

Melatonin can attenuate or prevent oxidative damage from EMF/RFR exposure. In an experiment exposing rats to microwave radiation (MW) from a GSM-900 mobile

phone with and without melatonin treatment to study renal impacts [25], the untreated exposed rats showed increases of lipid peroxidation markers as reduction of the activities of superoxide dismutase, catalase and glutathione peroxidase indicating decrement in antioxidant status. However these negative effects were inhibited in the exposed rats treated with melatonin. Melatonin also inhibited the emergence of preneoplastic liver lesions in rats exposed to EMFs [26]. The development of DNA strand breaks was observed in RFR exposed rats; this DNA damage was blocked by melatonin [27]. Exposure of cultured cortical neurons to EMF led to an increase in 8-hydroxyguanine in neuronal mitochondria, a common biomarker of DNA oxidative damage, along with a reduction in the copy number of mitochondrial DNA and the levels of mitochondrial RNA transcripts; but these effects could all be prevented by pretreatment with melatonin [7]. In a study of skin lesion induced by exposure to cell phone radiation, the skin changes in the irradiated group (which included thicker stratum corneum, epidermal atrophy, papillomatosis, basal cell proliferation, increased epidermal granular cell layer and capillary proliferation, impaired collagen tissue distribution and separation of collagen bundles in dermis) were prevented (except for hypergranulosis) by melatonin treatment [28]. Melatonin as well as caffeic acid phenylethyl ester (an antioxidant) both protected against retinal oxidative stress in rates exposed long-term to mobile phone irradiation [29]. Nitric oxide (NO) was increased in nasal and sinus mucosa in rats after EMF exposure, with this NO possibly acting as a defense mechanism suggesting tissue damage; but this was prevented by pretreatment with melatonin [30]. Melatonin treatment significantly prevented the increase in the MDA (malondyaldehyde, a marker of lipid peroxidation) content and XO (xanthine oxidase) activity in rat brain tissue after 40 days of exposure, but it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents [31].

Of note, the melatonin production of infants in isolettes in neonatal intensive care units appears to be impacted by the high ELF-EMF environment, in that when infants were removed from those exposures they showed an increase in melatonin levels [32]. There is an increased prevalence of ASCs in children who were born prematurely [33–43]. There are many potential prematurity-associated factors that could contribute to increased risk for ASCs, but proper melatonin regulation warrants EMF/RFR controls in the newborns' environment.

**2.1.2.3. Melatonin and autism.** Regarding melatonin status in people with ASCs, a recent meta-analysis summarized the current findings as indicating that “(1) Physiological levels of melatonin and/or melatonin derivatives are commonly below average in ASC and correlate with autistic behavior; (2) Abnormalities in melatonin-related genes may be a cause of low melatonin levels in ASD, and (3) . . . treatment with melatonin significantly improves sleep duration and sleep onset latency in ASD.” [44].

The meta-analysis also showed that polymorphisms in melatonin-related genes in ASC could contribute to lower melatonin concentrations or an altered response to melatonin, but only in a small percentage of individuals, since pertinent genes were found in only a small minority of those screened.

Based on the common presence of both sleep disorders and low melatonin levels, Bourgeron [45] proposed that synaptic and clock genes are important in ASCs, and that future studies should investigate the circadian modulation of synaptic function [45]. A number of melatonin-related genetic variants have been identified as associated with ASCs. Polymorphisms and deletions in the ASMT gene, which encodes the last enzyme of melatonin synthesis, have been found [46–48], and variations have been found as well for melatonin receptor genes [46,47,49]. CYP1A2 polymorphisms have been found in slow melatonin metabolisers, in whom melatonin levels are aberrant and initial response to melatonin for sleep disappeared in a few weeks [50].

*2.1.2.4. Autism AND melatonin AND glutathione.* Whereas PubMed searches for “autism AND melatonin” and “autism AND glutathione” each coincidentally yielded 72 citations, and “melatonin AND glutathione” yielded 803 citations, the search for “autism AND melatonin AND glutathione” yielded zero citations. This is interesting given the strong connection of melatonin and glutathione metabolically, as discussed above, alongside of the strongly established interest in both glutathione and melatonin in ASC research and increasingly in clinical practice. Hopefully one contribution of an investigation of EMF/RFR links to ASCs will be to help bring attention to this relationship, which may help identify potential environmental and physiological causes for low melatonin in those without pertinent mutations. Of pertinence, tryptophan hydroxylase (TPH2) – the rate limiting enzyme in the synthesis of serotonin, from which melatonin is derived – is extremely vulnerable to oxidation, and tends to misfold when its cysteine residues are oxidized, with the enzyme being converted to a redox-cycling quinoprotein [51–54].

### *2.1.3. Disturbed immune function*

There is by now a broad appreciation of the presence of immune disturbances in ASCs, to the point where there is an emerging discussion of ASCs as neuroimmune disorders [55,56]. Research identifying immune features in ASCs spans from genetics where risk genes have been identified to epigenetics where altered expression of immune genes is being reported as prominent in ASC epigenetics [57–59], and also includes prenatal infectious and immune disturbances as risk factors for autism as well as other neurodevelopmental and neuropsychiatric diseases as well as other conditions such as asthma [60–62]. Immune disturbances in infants and children with ASC are heterogeneous, with some but not all manifesting autoimmunity [63,64]. Anecdotally, recurrent infection is common while on the other hand some get sick less often than their peers. It is common for people with autism to

have family members with immune or autoimmune diseases [65]. The immune system is turning out to have an important role in brain development [66–68]. As mentioned, glial activation associated with brain immune response has been identified in a growing number of studies. Whether or not EMF/RFR contributes to these features of ASCs causally, based on the evidence below regarding immune impacts of EMF/RFR exposure [69], it is certainly plausible that such exposures could serve as aggravating factors.

*2.1.3.1. Low-intensity exposures.* The body's immune defense system is now known to respond to very low-intensity exposures [70]. Chronic exposure to factors that increase allergic and inflammatory responses on a continuing basis is likely to be harmful to health, since the resultant chronic inflammatory responses can lead to cellular, tissue and organ damage over time. Many chronic diseases are related to chronic immune system dysfunction. Disturbance of the immune system by very low-intensity electromagnetic field exposure is discussed as a potential underlying cause for cellular damage and impaired healing (tissue repair), which could lead to disease and physiological impairment [71,72]. Both human and animal studies report that exposures to EMF and RFR at environmental levels associated with new technologies can be associated with large immunohistological changes in mast cells as well as other measures of immune dysfunction and dysregulation. Mast cells not only can degranulate and release irritating chemicals leading to allergic symptoms; they are also widely distributed in the body, including in the brain and the heart, which might relate to some of the symptoms commonly reported in relation to EMF/RFR exposure (such as headache, painful light sensitivity, and cardiac rhythm and palpitation problems).

*2.1.3.2. Consequences of immune challenges during pregnancy.* As mentioned, infection in pregnancy can also increase the risk of autism and other neurodevelopmental and neuropsychiatric disorders via maternal immune activation (MIA). Viral, bacterial and parasitic infections during pregnancy are thought to contribute to at least 30% of cases of schizophrenia [73]. The connection of maternal infection to autism is supported epidemiologically, including in a Kaiser study where risk was associated with psoriasis and with asthma and allergy in the second trimester [65], and in a large study of autism cases in the Danish Medical registry [74] with infection at any point in pregnancy yielding an adjusted hazard ratio of 1.14 (CI: 0.96 – 1.34) and when infection occurred during second trimester the odds ratio was 2.98 (CI: 1.29 – 7.15). In animal models, while there is much variation in study design, mediators of the immune impact include oxidative stress, interleukin-6 and increased placental cytokines [61,68,75]. Garbett et al. [76] commented on several mouse models of the effects of MIA on the fetal brain that “The overall gene expression changes suggest that the response to MIA is a neuroprotective attempt by the



developing brain to counteract environmental stress, but at a cost of disrupting typical neuronal differentiation and axonal growth.” [76]. Maternal fetal brain-reactive autoantibodies have also been identified in some cases [62,77–82].

Although we have evidence of immune impacts of EMF/RFR, the impact of repeated or chronic exposure to EMF and RFR during pregnancy is poorly studied; could this trigger similar immune responses (cytokine production) and stress protein responses, which in turn would have effects on the fetus? Although this has been poorly studied, we do have data that very low cell phone radiation exposures during both human and mouse pregnancies have resulted in altered fetal brain development leading to memory, learning, and attention problems and behavioral problems [83].

*2.1.3.3. Potential immune contributions to reactivity and variability in ASCs.* Immune changes in ASCs appear to be associated with behavioral change [84–88], but the mechanisms are complex and to date poorly understood [89] and likely will need to be elucidated through systems biology methods that capture multisystem influences on the interactions across behavior, brain and immune regulation [90], including electrophysiology.

Two of the particularly difficult parts of ASCs are the intense reactivity and the variability in assorted symptoms such as tantrums and other difficult behaviors. Children with ASCs who also have gastrointestinal symptoms and marked fluctuation of behavioral symptoms have been shown to exhibit distinct innate immune abnormalities and transcriptional profiles of peripheral blood monocytes [91]. It is worth considering EMF/RFR exposures could be operating through related mechanisms so as to add to ‘allostatic loading’ in ways that exacerbate behavior. In Johansson 2006 and 2007 a foundation is provided for understanding how chronic EMF/RFR exposure can compromise immune function and sensitize a person to even small exposures in the future [72,92]. Johansson discusses alterations of immune function at environmental levels resulting in loss of memory and concentration, skin redness and inflammation, eczema, headache, and fatigue. Mast cells that degranulate under EMF and RFR exposures and substances secreted by them (histamine, heparin and serotonin) may contribute to features of this sensitivity to electromagnetic fields [92]. Theoharides and colleagues have argued that environmental and stress related triggers might activate mast cells, causing inflammatory compromise and leading to gut–blood–brain barrier compromise, seizures and other ASC symptoms [93,94], and that this cascade of immune response and its consequences might also be triggered in the absence of infection by mitochondrial fragments that can be released from cells in response to stimulation by IgE/anti-IgE or by the proinflammatory peptide substance P [95].

Seitz et al. [96] reviewed an extensive literature on electromagnetic hypersensitivity conditions reported to include sleep quality, dizziness, headache, skin rashes, memory and concentration impairments related to EMF and RFR [96].

Some of these symptoms are common in ASCs, whether or not they are due to EMF/RFR exposure, and the experience of discomfort may be hard to document due to difficulties with self-reporting in many people with ASCs.

Johansson [72] also reports that benchmark indicators of immune system allergic and inflammatory reactions occur under exposure conditions of low-intensity non-ionizing radiation (immune cell alterations, mast cell degranulation histamine-positive mast cells in biopsies and immunoreactive dendritic immune cells) [71,72]. In facial skin samples of electro-hypersensitive persons, the most common finding is a profound increase in mast cells as monitored by various mast cell markers, such as histamine, chymase and tryptase [97]. In ASCs, infant and childhood rashes, eczema and psoriasis are common, and they are common in family members as well [98].

#### *2.1.4. Alteration of and damage to cells in the brain*

Brain cells have a variety of ways of reacting to environmental stressors, such as shape changes, metabolic alterations, upregulation or downregulation of neurotransmitters and receptors, other altered functionality, structural damage, production of un-metabolizable misfolded proteins and other cellular debris, and apoptosis; these range along a spectrum from adaptation to damage and cell death. These types of alterations can be looked at in animals under controlled conditions, but in human beings direct cellular examination can only be done on surgical biopsy tissue – which is hardly ever available in people with ASCs – or after death, at which point there has been a whole lifetime of exposures that are generally impossible to tease apart if there were even motivation to do so. This complicates the comparison of brain cell and tissue-related pathophysiology between what is seen in ASCs and what is associated with EMF/RFR exposures.

*2.1.4.1. Brain cells.* Impact of EMF/RFR on cells in the brain has been documented by some of the studies that have examined brain tissue after exposure, although the interpretation of inconsistencies across studies is complicated by sometimes major differences in impact attributable to differences in frequencies and duration of exposure, as well as to differences in resonance properties of tissues and other poorly understood constraints on cellular response. These studies and methodological considerations have been reviewed in depth in several sections of the 2012 BioInitiative Report [11,99]. A few examples of observations after exposure have included dark neurons (an indicator of neuronal damage), as well as alteration of neuronal firing rate [100], and upregulation of genes related to cell death pathways in both neurons and astrocytes [101]. Astrocytic changes included increased GFAP and increased glial reactivity [102–105], as well as astrocyte-pertinent protein expression changes detected by Fragopoulou et al. [322] as mentioned above. Also observed has been a marked protein downregulation of the nerve growth factor glial maturation factor beta (GMF) which is

considered as an intracellular signal transduction regulator in astrocytes, which could have significant impact on neuronal-glial interactions as well as brain cell differentiation and tumor development. Diminution of Purkinje cell number and density has also been observed, [106] including in two studies of the impacts of perinatal exposure [107,108]. Promotion of pro-inflammatory responses in EMF-stimulated microglial cells has also been documented [109].

Neuropathology findings in ASCs have been varied and have been interpreted according to various frameworks ranging from a regionalized approach oriented to identifying potential brain relationships to ASC's behavioral features [110] to identifying receptor, neurotransmitter and interneuron abnormalities that could account for an increased excitation/inhibition ratio [111–115]. Studies have documented a range of abnormalities in neurons, including altered cellular packing in the limbic system, reduced dendritic arborization, and reductions in limbic GABAergic systems [116]. Over the past decade a shift has occurred from presuming that all pertinent brain changes occurred prior to birth, to an acknowledgement that ongoing cellular processes appear to be occurring not only after birth but well into adulthood [117]. One of the reasons for this shift was the observation that head size (as well as brain weight and size) was on average larger in children with autism, and the head sizes of children who became diagnosed with autism increased in percentile after birth [118].

**2.1.4.2. Neuroinflammation, glial activation and excitotoxicity.** Although much attention has been paid in ASC brain literature to specific regions manifesting differences in size and activity in comparison to those without ASCs, there are other observations that are not strictly regional in nature, such as more widely distributed scaling differences (e.g. larger brains, wider brains, increased white matter volume, along with altered functional connectivity and coherence to be discussed below). Recently more studies have appeared identifying pathophysiological abnormalities such as neuroinflammation, mitochondrial dysfunction and glutathione depletion in brain tissue. Neuroinflammation was first identified in a study of postmortem samples from eleven individuals aged 5–44 who had died carrying an ASC diagnosis, in which activated astrocytes and microglial cells as well as abnormal cytokines and chemokines were found. Other research has identified further astrocyte abnormalities such as altered expression of astrocyte markers GFAP abnormalities, with elevation, antibodies, and altered signaling having been documented [119–121]. Increased microglia activation and density as well as increased myeloid dendritic cell frequencies have also been documented [87,122,123], as has abnormal microglial-neuronal interactions [124]. Recently, through use of the PET ligand PK11105, microglial activation was found to be significantly higher in multiple brain regions in young adults with ASCs [125]. Genes associated with glial activation have been documented as upregulated.

Garbett et al measured increased transcript levels of many immune genes, as well as changes in transcripts related to cell communication, differentiation, cell cycle regulation and chaperone systems [126]. Voineaugu and colleagues performed transcriptomic analysis of autistic brain and found a neuronal module of co-expressed genes which was enriched with genetically associated variants; an immune-glial module which showed no such enrichment for autism GWAS signals was interpreted as secondary [127], but this seems to involve circular thinking, since it implies that the primary cause must be genetic, which is an assumption deriving from a dominant model, but is not a proven fact.

Neuroinflammation also does not appear to be strictly localized in a function-specific fashion, and it may contribute both to more broadly distributed and more focal features for tissue-based reasons. It may be that brain regions with particular prominence in ASCs may have distinctive cellular characteristics—e.g. the amygdala [128–138], which may have a larger or more reactive population of astrocytes [139] or the basal ganglia which may have greater sensitivity to even subtle hypoxia or perfusion abnormalities. In this case it may be the histology of these areas that makes them vulnerable to environmental irritants, and this may contribute to how environmental factors such as EMF/RFR might trigger or aggravate some of ASC's features. More widely distributed brain tissue pathology be part of what leads to differences in ASCs in brain connectivity. However these types of tissue-function relationships have been poorly investigated. Belyaev has intensively reviewed physical considerations including the contribution of tissue differences to variability in measured EMF/RFR impacts [11].

Various signs of mitochondrial dysfunction and oxidative stress have also been identified in the brain. Findings include downregulation of expression of mitochondrial electron transport genes [140] or deficit of mitochondrial electron transport chain complexes [141], brain region specific glutathione redox imbalance [142], and evidence of oxidative damage and inflammation associated with low glutathione redox status [143]. Oxidative stress markers were measured as increased in cerebellum [144].

Additional support for the presence of tissue pathophysiology-based changes in brains of people with ASCs comes from the various studies documenting reduction in Purkinje cell numbers [117,145–150], possibly due to oxidative stress and an increased excitation/inhibition ratio that could potentially be acquired [150]. Also of note are changes in the glutamatergic and GABAergic systems, which when imbalanced can disturb the excitation/inhibition ratio and contribute to seizure disorders; reductions in GABA receptors as well as in GAD 65 and 67 proteins that catalyse the conversion of glutamate into GABA have been measured [151–153]. A consensus statement on the cerebellum in ASCs stated that, “*Points of consensus include presence of abnormal cerebellar anatomy, abnormal neurotransmitter systems, oxidative stress, cerebellar motor and cognitive deficits, and neuroinflammation in subjects with autism*” [150].

Some indirect corroboration for these findings has come from neuroimaging, where the initial hypothesis regarding the tissue basis of the larger size of brains in so many people with autism – that it was due to a higher density of neurons and more tightly packed axons – came under question with the emergence of contradictory findings, well reviewed a few years ago by Dager and colleagues [154]. These include reduced rather than increased density of NAA (*n*-acetylaspartate, a marker of neuronal integrity and density that is produced in the mitochondria), reduced rather than increased fractional anisotropy suggesting less tightly packed axonal bundles [155–161] and greater rather than lower diffusivity, all of which may be more consistent with lower density of tissue and tissue metabolites and more fluid, which could be consistent with neuroinflammation and/or oxidative stress. The early postnatal development of such lower fractional anisotropy and increased diffusivity was measured in the process of occurring recently, in the first large prospective longitudinal imaging study of infants, who trended from 6 months to 2 years in the direction of these findings becoming more pronounced—but still with substantial overlap with those infants who did not develop autism [160]. This trend was consistent with prior studies showing increase in head size after birth, and added some information about what was happening in the brain to drive this size increase, although due to its methods it could only indirectly address the possibility that emergence during the first few years of life of tissue pathophysiology disturbances such as neuroinflammation might be contributing to these trends [162].

There is also substantial variability across many different types of brain findings. Of interest is that a number of functional brain imaging and electrophysiology studies have identified greater heterogeneity in response to stimuli between individuals in the ASC group than individuals in the neurotypical control group [163,164]. This may make more sense from the point of view of non-linear response—i.e. a disproportionality between output and input (as well as state and context sensitivity), in a pathophysiologically perturbed brain system. Nonlinearity has also been a significant methodological issue in EMF/RFR research because linear methods of study design and data analysis have often been insensitive to effects, whereas nonlinear methods have been argued to show greater sensitivity [165–175].

It is important to entertain how environmental agents could contribute individually and synergistically to brain changes in ASCs, how different exposures may disturb physiology similarly or differently, and how these changes may develop over progress over time after the earliest periods in brain development. EMF/RFR exposures could be pre-conceptional, prenatal or postnatal—or all of the above; it is conceivable that this could be the case in ASCs as well.

**2.1.4.3. Altered development.** There is some evidence for altered brain and organism development in relation to EMF/RFR exposure. Aldad et al. [83] exposed mice in-utero

to cellular telephones, with resultant aberrant miniature excitatory postsynaptic currents, and dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex [83]. Lahijani exposed preincubated chicken embryos to 50 Hz EMFs, and made the following morphological observations: “*exencephalic embryos, embryos with asymmetrical faces, crossed beak, shorter upper beak, deformed hind limbs, gastroschisis, anophthalmia, and microphthalmia. H&E and reticulin stainings, TEMS, and SEMs studies indicated EMFs would create hepatocytes with fibrotic bands, severe steatohepatitis, vacuolizations, swollen and extremely electron-dense mitochondria, reduced invisible cristae, crystalized mitochondria with degenerated cristae, myelin-like figures, macrophages engulfing adjacent cells, dentated nuclei, nuclei with irregular envelopes, degenerated hepatocytes, abnormal lipid accumulations, lipid droplets pushing hepatocytes’ nuclei to the corner of the cells, abundant cellular infiltrations cellular infiltrations inside sinusoid and around central veins, disrupted reticulin plexus, and release of chromatin into cytosol, with partially regular water layers, and attributed cell damage to elevated free radical induced cell membrane disruptions*” [5].

Although it is of great interest to characterize the changes in development associated with ASCs, it is also difficult to do in human beings because at present diagnosis is not possible until at least 2–3 years after birth. By now there have been a lot of prospective studies of infants at high risk for autism, but the in vivo brain imaging and electrophysiology data from these studies is only starting to be published, and so the for now the main sources of information are still inference backwards from post-mortem or imaging data, and animal models, both of which have clear limitations. Thus it is impossible to seek precise parallels here between what we know about the development of ASCs compared with the impacts of EMF/RFR exposures.

Nevertheless it is of real concern that such exposures have elicited some of the brain tissue changes that have been documented in ASCs, both in early development and subsequently. Already noted above is the question of whether high exposures of neonates to monitoring equipment may affect the melatonin levels of neonates [32]; these exposures also impact heart rate variability [258]. There are no studies yet on infants exposed to baby surveillance monitors or DECT wireless phones. However there are good laboratory testing studies yielding actual measurements of these devices that conclude: “*Maximum incident field exposures at 1 m can significantly exceed those of base stations (typically 0.1–1 V/m). At very close distances the derived or reference exposure limits are violated for baby surveillance monitors and DECT phones. Further, the authors conclude that, based on very strictly controlled laboratory testing of everyday devices like baby monitors and some cordless phones (W)orse case peak spatial SAR values are close to the limit for the public or uncontrolled environments, e.g., IEEE 802.11b and Bluetooth Class I*” [176].

Even exposure of the fetus to laptop computer wireless emissions through the pregnant mother's use of this device on her lap may involve induction of strong intracorporeal electric current densities from the power supply possibly even more than the device itself [177].

**2.1.4.4. Brain blood flow and metabolism.** Cerebral perfusion and metabolism abnormalities have been identified in close to two dozen papers studying autistic cohorts. Cerebral perfusion refers to the quantity of blood flow in the brain. Abnormal regulation of cerebral perfusion is found in a range of severe medical conditions including tumors, vascular disease and epilepsy. Cerebral hypoperfusion has also been found in a range of psychiatric disorders [178]. Neurocognitive hypotheses and conclusions, as well as localization of perfusion changes, have been heterogeneous across these papers. Hypoperfusion or diminished metabolism has been identified in frontal regions [179–184], temporal lobes [179,181,183–190], as well as a variety of subcortical regions including basal ganglia [181,188,189], cerebellum [188], limbic structures [184,191] and thalamus [188,189,191]—i.e. in a widely distributed set of brain regions. Possibly because virtually all of these studies were oriented toward testing neuropsychological rather than pathophysiological hypotheses, there were no probes or tests reported to unearth the tissue level alterations that might be underlying these reductions in blood flow in these brains.

While a large number of animal studies have documented blood–brain barrier (BBB) abnormalities from EMF/RFR exposures, only a few PET studies have been performed evaluating EMF exposure effects upon brain glucose metabolism. Volkow et al. performed PET scans both with and without EMF exposure (50 min of GSM-900 with maximum SAR of 0.901 W/kg), and the participants were blinded to the exposure situation [192]. A 7% increase in metabolism in the exposure situation compared to controls was identified regionally on the same side of the head as where the mobile phone was placed. The strength of the E-field from the phones correlated positively with the brain activation, which the authors hypothesized was from an increase in brain neuron excitability. A subsequent smaller study by Kwon et al. demonstrated not increased but decreased brain  $^{18}\text{F}$ FDG uptake after GSM-900 exposure [193].

Many possible mechanisms could be involved in the metabolic and perfusion abnormalities identified, ranging from altered neuronal activity that was hypothesized in the Volkow et al. [192]  $^{18}\text{F}$ FDG PET study to narrowing of vascular lumen in the setting of reduced perfusion. Underlying tissue pathophysiology-based phenomena could influence the measurable metabolism and perfusion abnormalities, via mechanisms such as excitotoxicity, cell stress response, constriction of capillary lumen by activated astrocytes, volume effects of vascular extravasation, subtle alterations in blood viscosity due to immune or oxidative stress-associated blood chemical changes, with other possibilities

as well. Differences in findings between papers could relate at least in part to study design and nonlinearity issues.

#### 2.1.5. Electrophysiology perturbations

At this stage the argument we hit a key pivot point, where we look at how the alterations in molecular, cellular and systems physiological function, which occur in the brain as well as in the body, impact the transduction into the electrical signaling activities of the brain and nervous system. Certainly the cells and tissues whose physiological challenges we have already discussed provide the material substrate for the electrical activity. Although ASC behaviors are influenced by many factors, they must in principle be mediated through nervous system electrophysiology.

If the cells responsible for generating synapses and oscillatory signaling are laboring under cellular and oxidative stress, lipid peroxidation, impaired calcium and other signaling system abnormalities, then mitochondrial metabolism will fall short, all the more so because of the challenges from the immune system which in turn be triggered to a major extent by environment. How well will synaptic signals be generated? How well will immune-activated and thereby distracted glial cells be able to modulate synaptic and network activity? [194–197].

At present we are in the early stages of being able to formulate these questions well enough to address them empirically. We do know that microglial activation can impact excitatory neurotransmission mediated by astrocytes [198]. We do know that the cortical innate immune response increases local neuronal excitability and can lead to seizures [199,200]. We do know that inflammation can play an important role in epilepsy [201]. We know less about lower levels of chronic or acute pathophysiological dysfunction and how they may modulate and alter the brain's electrophysiology.

**2.1.5.1. Seizures and epilepsy.** EEG signals in ASCs are abnormal on a variety of levels. At the most severe level, EEGs show seizure activity. Although less than 50% of people with ASCs clearly have seizures or epilepsy a much larger number have indications of epileptiform activity, and an even larger percent have subclinical features that can be noted by a clinical epileptologist though not necessarily flagged as of clinical concern. In addition to the association of some severe epilepsy syndromes (e.g. Landau Kleffner, tuberous sclerosis) with autism, the risk of epilepsy is substantially higher in people with ASCs than in the general population, with a large subset of these individuals experiencing seizure onset around puberty, likely in relation to aberrations in the dramatic and brain-impactful hormonal shifts of that phase of life. Epileptic seizures can be both caused by and cause oxidative stress and mitochondrial dysfunction. Seizures can cause extravasation of plasma into brain parenchyma [202–206] which can trigger a vicious circle of tissue damage from albumin and greater irritability, as discussed above. Evidence suggests that if a BBB is already disrupted, there



will be greater sensitivity to EMF/RFR exposure than if the BBB were intact [207,208], suggesting that such exposures can further exacerbate vicious circles already underway.

The combination of pathophysiological and electrophysiological vulnerabilities has been explored in relation to the impact of EMF/RFR on people with epilepsy. EMF/RFR exposures from mobile phone emissions have been shown to modulate brain excitability and to increase interhemispheric functional coupling [209,210]. In a rat model the combination of picrotoxin and microwave exposure at mobile phone-like intensities led to a progressive increase in neuronal activation and glial reactivity, with regional variability in the fall-off of these responses three days after picrotoxin treatment [211], suggesting a potential for interaction between a hyperexcitable brain and EMF/RFR exposure.

One critical issue here is nonlinearity and context and parameter sensitivity of impact. In one study, rat brain slices exposed to EMF/RFR showed reduced synaptic activity and diminution of amplitude of evoked potentials, while whole body exposure to rats led to synaptic facilitation and increased seizure susceptibility in the subsequent analysis of neo-cortical slices [212]. Another study unexpectedly identified enhanced rat pup post-seizure mortality after perinatal exposure to a specific frequency and intensity of exposure, and concluded that apparently innocuous exposures during early development might lead to vulnerability to stimuli presented later in development [213].

**2.1.5.2. Sleep.** Sleep involves a profound change in brain electrophysiological activity, and EEG abnormalities including disrupted sleep architecture figure in sleep challenges in ASCs. Sleep symptoms include bedtime resistance, sleep onset delay, sleep duration and night wakings; and sleep architecture can involve significantly less efficient sleep, less total sleep time, prolonged sleep latency, and prolonged REM latency [214,215], with these sleep problems being worse in children with ASCs who regressed than in those who did not regress into their autism [215]. EEG abnormalities have also been associated with EMF/RFR exposure, including disrupted sleep architecture as well as changes in sleep spindles and in the coherence and correlation across sleep stages and power bands during sleep [216,217].

Sleep disturbance symptoms are also common in both situations. Insomnia is commonly reported in people who are chronically exposed to low-level wireless antenna emissions. Mann and Rosch reported an 18% reduction in REM sleep, which is key to memory and learning functions in humans [321]. In ASCs sleep difficulties are highly pervasive and disruptive not only to the affected individual but also to their whole family due to the associated problems such as noise (e.g. screaming at night) and the need for vigilance.

The multileveled interconnections involved in the modulation of sleep exemplify the interconnectedness of the many levels of pathophysiology reviewed here: “*Extracellular ATP associated with neuro- and glia-transmission, acting via purine type 2 receptors, e.g., the P2X7 receptor, has a role*

*in glia release of IL1 and TNF. These substances in turn act on neurons to change their intrinsic membrane properties and sensitivities to neurotransmitters and neuromodulators such as adenosine, glutamate and GABA. These actions change the network input-output properties, i.e., a state shift for the network*” [218]. With disturbance simultaneously at so many of these levels, it is not surprising that sleep dysregulation is nearly universal in ASCs, and common in the setting of EMF/RFR exposures.

**2.1.5.3. Quantitative electrophysiology.** While clinical reading of EEG studies is done visually, a growing number of studies are examining EEG and MEG data using digital signal processing analysis to find not only epilepsy, but also abnormalities in the power spectrum, i.e. the distribution of power over the different frequencies present, with some studies showing impaired or reduced gamma-and activity [219–221] and others showing reduction of spectral power across all bands [222] while still others showed increased high-frequency oscillations [223]. Abnormalities in coherence and synchronization between various parts of the brain have been found [224–226], comparable to abnormal functional connectivity measured by fMRI [227] but measurable with higher temporal resolution using EEG or MEG [228–232]. Several studies have identified reduced complexity and increased randomness in EEGs of people with ASCs [233,234], as well as an increase in power but a reduction in coherence [229,235]. Some electrophysiological metrics are emerging as potential discriminators between brain signal from individuals with ASCs and those who are neurotypical, such as a wavelet-chaos-neural network methodology applied to EEG signal [236] and reduced cross-frequency coupling [237].

EMF/RFR also has impacts at levels of brain function measurable by these techniques. At various frequencies and durations of exposure it has been noted to impact alpha and beta rhythms [238], to increase randomness [170,239], to alter power, to modulate interhemispheric synchronization [240], to alter electrical activity in brain slices [241] and to alter the patterns of coordination (spectral power coherence) across the major power bands [242]. Bachman et al. [243] showed statistically significant changes in EEG rhythms and dynamics occurred in between 12% and 20% of healthy volunteers [243]. In children, exposures to cell phone radiation have resulted in changes in brain oscillatory activity during some memory tasks [97,102].

**2.1.5.4. Sensory processing.** Symptomatic level issues with sensory processing are highly prevalent in ASCs and can include hypersensitivity to external stimuli, hyposensitivity to internal sensations and difficulty localizing sensation including pain, and difficulty processing more than one sensory channel at one time [244–246]. There is now electrophysiological evidence of abnormalities at early (brainstem) stages of sensory processing, as well as in later stages of processing that occur in the cortex [247]. Some studies have

shown lower and some longer latencies of response to an auditory stimulus [247]. Domains of perception where the performance of people with ASCs is superior to that of neurotypical individuals have been identified [248]. *“It is ... probable that several mechanisms and neuronal abnormalities, most likely at multiple levels (from single neurons through to inter-area connections), all contribute to varying degrees to the abnormal sensory processing observed in ASD. It is also likely that no single mechanism is unique to one sensory modality, which is why we see such a widely distributed range of abnormalities across modalities”* [247].

It is also possible that the mechanisms may not simply be neural—they may also be modulated by glial, metabolic, immune, perfusional and other physiological processes by common underlying cellular abnormalities, and by physical properties as well. Yet there are few studies focusing upon the interface of tissue pathophysiology with electrophysiology.

Kenet et al. demonstrated environmental vulnerability of sensory processing in the brain by the exposure of rat dams to noncoplanar polychlorinated biphenyls (PCBs), during gestation and for three subsequent weeks of nursing [247]. The rat pups showed normal hearing sensitivity and brainstem auditory responses, but their tonotopic development of the primary auditory cortex was grossly distorted [249]. This study may be particularly relevant for EMF/RFR exposures, as Pessah, a co-author on this Kenet et al. [249] paper, was cited earlier as documenting how the noncoplanar PCBs used in this experiment target calcium signaling as do EMF/RFR exposures—i.e. they both converge upon a common particularly critical cellular mechanism [250,251].

**2.1.5.5. Autonomic dysregulation.** Although there are a fair number of negative studies regarding the impact of EMF/RFR exposure on the autonomic nervous system, increased HRV and autonomic disturbances have been documented [252–256]. Buchner and Eger [257], in a study in rural Germany of the health impacts of exposures from a new base station yielding novel exposure to EMF/RFR, saw a significant elevation of the stress hormones adrenaline and noradrenaline during the first six months with a concomitant drop in dopamine, with a failure to restore the prior levels after a year and a half. These impacts were felt by the young, the old and the chronically ill, but not by healthy adults [257].

Neonate vulnerability was documented by Bellieni et al. [258] who found that heart rate variability is adversely affected in infants hospitalized in isolettes or incubators where ELF-EMF levels are in the 0.8 to 0.9  $\mu$ T range (8 to 9 mG). Infants suffer adverse changes in heart rate variability, similar to adults [258]. This electromagnetic stress may have lifelong developmental impacts, based on a study showing that in-utero beta 2 agonist exposure can potentially induce a permanent shift in the balance of sympathetic-to-parasympathetic tone [259].

Meanwhile clinical observation and a growing body of literature support a major role for stress in ASCs [260–263],

with variability amongst individuals in the severity of the stress response but a tendency to have high tonic sympathetic arousal at baseline [264–269].

The impact of EMF/RFR exposure can also be greatly influenced by the stress system status of the individual being exposed. Tore et al. sympathectomized some of his rats before exposure to GSM, to simulate cell phone exposure [207,208]. Sympathectomized rats, which were in a chronic inflammation-prone state, had more prominent albumin leakage than sham-exposed rats. However in the sympathectomized rats who were exposed to GSM, albumin leakage was greatly increased, to levels resembling those observed in positive controls after osmotic shock. Salford et al. [99] suggest that *“...more attention should be paid to this finding, since it implicates that the sensitivity to EMF-induced BBB permeability depends not only on power densities and exposure modulations, but also on the initial state of health of the exposed subject”* [99].

The interconnection between stress and brain connectivity (or coherence) in ASCs is brought out by Narayanan et al. in a pilot study testing the impact of the beta blocker propranolol on brain functional connectivity measured using functional MRI [270]. A fairly immediate increase in functional connectivity was noted from propranolol—but not from nadolol which has the same vascular effects but does not cross the BBB. Propranolol decreases the burden of norepinephrine, thereby reducing the impact of stress systems on brain processing, and the authors interpreted these effects as creating an improvement of the brain's signal-to-noise ratio [271], allowing it to utilize and coordinate more remote parts of its networks. This suggests that stressors such as EMF/RFR, by adding biologically non-meaningful noise to the system, might have the opposite effects, degrading coherent integration.

## 2.2. De-tuning of the brain and organism

### 2.2.1. Electromagnetic signaling, oscillation and synchrony are fundamental, and vulnerable

While electrophysiological activity is an intrinsic property of the nervous system, electromagnetic signaling is a vital aspect of every cell and of molecular structure.

All life on earth has evolved in a sea of natural low-frequency electromagnetic (EM) fields. They originate in terrestrial and extraterrestrial sources. The ever-growing use of electric power over the last century has sharply modified this natural environment in urban settings. Exposure to power-frequency fields far stronger than the natural environment is now universal in civilized society. [272]

Adey published some of the earliest scientific studies on the “cooperativity” actions of cells in communication. Studies showing us that the flux of calcium in brain tissue and immune cells is sensitive to ELF-modulated radiofrequency fields is actually telling us that some of the most fundamental properties of cells and thus of our existence can be modulated by EMF/RFR. *“...in first detection of environmental*

*EM fields in tissues, there appears to be a general consensus that the site of field action is at cell membranes. Strands of protein are strategically located on the surface of cells in tissue, where they act as detectors of electrical and chemical messages arriving at cell surfaces, transducing them and transmitting them to the cell interior. The structural basis for this transductive coupling by these protein strands is well known. Through them, cell membranes perform a triple role, in **signal detection, signal amplification, and signal transduction to the cell interior**" [272].*

Oscillation is also a universal phenomenon, and biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels [273,274]. The key to synchronization is the joint actions of cells that co-operate electrically - linking populations of biological oscillators that couple together in large arrays and synchronize spontaneously according to the mathematics described for Josephson junctions (Brian Josephson, the 1993 Nobel prize winner for this concept). This concept has been professionally presented in journal articles and also popularized in a book by Prof. Steven Strogatz, a mathematician at Cornell University who has written about 'sync' as a fundamental organizing principle for biological systems [274,275]. "*Organisms are biochemically dynamic. They are continuously subjected to time-varying conditions in the form of both extrinsic driving from the environment and intrinsic rhythms generated by specialized cellular clocks within the organism itself. Relevant examples of the latter are the cardiac pacemaker located at the sinoatrial node in mammalian hearts and the circadian clock residing at the suprachiasmatic nuclei in mammalian brains. These rhythm generators are composed of thousands of clock cells that are intrinsically diverse but nevertheless manage to function in a coherent oscillatory state. This is the case, for instance, of the circadian oscillations exhibited by the suprachiasmatic nuclei, the period of which is known to be determined by the mean period of the individual neurons making up the circadian clock. The mechanisms by which this collective behavior arises remain to be understood*" [274].

The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles. Others have discussed how this also applies to mitochondria: "*Organisation of mitochondrial metabolism is a quintessential example of a complex dissipative system which can display dynamic instabilities. Several findings have indicated that the conditions inducing instabilities are within the physiological range and that mild perturbations could elicit oscillations. Different mathematical models have been put forth in order to explain the genesis of oscillations in energy metabolism. One model considers mitochondria as an organised network of*

*oscillators and indicates that communication between mitochondria involves mitochondrial reactive oxygen species (ROS) production acting as synchronisers of the energy status of the whole population of mitochondria. An alternative model proposes that extramitochondrial pH variations could lead to mitochondrial oscillations*" [276].

Mitochondrial dysfunction is important in ASCs but is usually conceptualized in purely biochemical terms without mentioning any oscillatory dimension to mitochondrial activity; it is conceivable that the interplay between biochemistry and oscillation could figure significantly in the mechanisms of impact of EMF/RFR in ASCs.

The field of bioelectromagnetics has studied exposure to very low levels of electromagnetic frequencies. Exposures can alter the magnetokinetics of the formation of a chemical bond, shifting the rate and amount of product produced [272].

Not just chemical reactions but synchronous biological oscillations in cells (pacemaker cells) can be disturbed and disrupted by artificial, exogenous environmental signals, which can lead to desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles [277]. Buzsaki in his book *Rhythms of the Brain* says "*rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance*." [273].

Disturbance can get increasingly disruptive as more damage occurs and more systems are thrown out of kilter and out of cooperativity. One can think of the kindling model in which repeated induction of seizures leads to longer and more severe seizures and greater behavioral involvement. The combination of disruptive and stimulatory effects of biologically inappropriate EMF/RFR exposures could contribute to disruption of synchronized oscillation and cooperativity at a myriad of levels but particularly in the brain, and this may contribute to the loss of coherence and complexity in the brain in autism, as well as dysregulation of multiple other bodily systems. Strogatz points out that there are many more ways of being desynchronized than of being synchronized [274] (which may relate to ASC's great heterogeneity). It has even been suggested that autism itself could be due to brain desynchronization [278].

### 2.2.2. Behavior as an "emergent property"

From a pathophysiological point of view one might hypothesize that a brain with greater indications of oxidative stress along with immune activation and mitochondrial dysfunction might generate different oscillatory activity than a brain in which those pathophysiological features were absent. From this vantage point it would make sense to propose that the compromised whole body health status of at least many with ASCs would make it harder for them to maintain the resilience of their brain cells and brain activities in the face of potentially disruptive exposures. Yet the investigation of how this might occur remains a largely unexplored frontier. But



from the point of view of making sense of the brain impact of environmental challenges – including but not limited to EMF-RFR – this investigation is crucial.

The pathophysiological perspective that guides this review would suggest a move away from considering the behavioral manifestations of ASCs as core, intrinsic, ‘hard-wired traits.’ *Instead behaviors may be better understood as ‘outputs’ or emergent properties – what the brain and body produce – when their physiological attributes are altered* in these fashions for whatever reasons—be they genetic, environmental or many combinations of both [279–284]. Sleep and consciousness have also been considered ‘emergent properties’ [285,286]. Brain oscillatory activity is critical for organizing behavior, and it arises from cells and subcellular features that are shaped by the environment and can act differently based on their functional status as well as on account of external sensory or psychosocial stimuli.

In particular, (a) brain oscillatory activity is intimately connected with underlying cellular, metabolic and immune status, (b) EMF/RFR is capable of perpetrating changes at each of these levels, and (c) problems at each of these levels can make other problems worse. And as mentioned earlier, EMF/RFR and various toxicants can co-potentiate damage [287–294], amplifying ‘allostatic load’.

Put together, all of this implies that the combination of these EMF/RFR impacts may quite plausibly significantly contribute both to how ASCs happen in individuals and to why there are more reported cases of ASCs than ever before (1200–1500% increase in reported cases over the past 15–20 years, with studies showing that a substantial portion of this increase (45–65%) cannot be written off as artifact and may well represent true increases [295,296]).

The hopeful side of this framing of the problem comes from moving beyond the increasingly anachronistic idea that autism is determined overwhelmingly by genetic code about which we can do little or nothing. An emerging model that explains much more of what we now know frames ASCs as the dynamic, active outcomes of perturbed physiological processes – again, more like a chronic but changeable ‘state’ than a ‘trait.’ In the latter model, one is empowered – and motivated – to strongly reduce exposures and to make aggressive constructive environmental changes – particularly in diet and nutrition, given their protective potency discussed above [297]. In this way ‘allostatic load’ can be reduced, physiological damage can be repaired, homeostasis can be restored and resilience and optimal function can be promoted.

### 3. Implications

#### 3.1. Exposures and their implications

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR [298,299]. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss

of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice [83].

##### 3.1.1. Exposures have outpaced precautions

There is no question that huge new exposures to EMF/RFRs have occurred over the past few decades. As discussed extensively in the BioInitiative 2012 update [299], there is much concern that regulations to date have been based on a very limited sense of the pertinent biology, and particularly that limiting concern to thermal impacts is no longer valid since there is a wealth of evidence by now that non-thermal impacts can be biologically very powerful. Only in the last two decades have exposures to RFR and wireless technologies become so widespread as to affect virtually every living space, and affect every member of societies around the world. Even as some disease patterns like brain tumors from cell phone use have become ‘epidemiologically visible’, there are no comprehensive and systematic global health surveillance programs that really keep up to report EMF/RFR health trends [300].

The deployment of new technologies is running ahead of any reasonable estimation of possible health impacts and estimates of probabilities, let alone a solid assessment of risk. However, what has been missing with regard to EMF/RFR has been an acknowledgement of the risk that is demonstrated by the scientific studies. There is clear evidence of risk, although the magnitude of the risk is uncertain, and the magnitude of doing nothing on the health effects cost to society is similarly uncertain. This situation is very similar to our history of dealing with the hazards of smoking decades ago, where the power of the industry to influence governments and even conflicts of interest within the public health community delayed action for more than a generation, with consequent loss of life and enormous extra health care costs to society. [301].

##### 3.1.2. The population’s exposure has increased

The very rapid global deployment of both old and new forms of emerging wireless technologies in the last two decades needs aggressive evaluation from a public health perspective, given the range of physiological impacts described in Section 2.

In the United States, the deployment of wireless infrastructure (cell tower sites) to support cell phone use has accelerated greatly in the last decades. The Cellular Telephone Institute of America (CTIA) estimated that in 1997 there were only 36,650 cell sites in the US; but increased rapidly to 131,350 in June 2002; 210,350 in June 2007 and 265,561 in June 2012 [302,303]. About 220,500 cell sites existed in 2008 [303–305]. These wireless facilities for cellular phone voice



and data transmission produce RFR over broad areas in communities and are an involuntary and unavoidable source of whole-body radiofrequency radiation exposure. Other new RFR exposures that did not exist before are from WI-FI access points (hotspots) that radiate 24/7 in cafes, stores, libraries, classrooms, on buses and trains, and from personal WI-FI enabled devices (iPads, tablets, PDAs, etc).

Not surprisingly, the use of cell phones has a parallel growth trend. In the late 1980s and early 1990's, only a few percent of the US population were cell phone users. By 2008, eighty-four percent (84%) of the population of the US owned cell phones. CTIA reports that wireless subscriber connections in the US increased from 49 million in June 1997 to 135 million in June 2002 to 243 million in June 2007 to 322 million in June 2012 [302,303]. This represents more than a 100% penetration rate in the US consumer market, up from just a few percent in the early 1990's. The number of wireless subscribers in June 1997 was 18%; in June 2002 it was 47%; in June 2007 it was 81% and in June 2012 it was 101%.

The annualized use of cell phones in the US was estimated to be 2.23 trillion minutes in 2008 and 2.296 trillion minutes in 2010 [303]. There are 6 billion users of cell phones worldwide in 2011 up from 2.2 billion in 2008 and many million more users of cordless phones.

The number of US homes with *only* wireless cell phones has risen from 10.5% in 2007 to 31.6% in June of 2012 [302,303]. There are no statistics for June 1997 nor for June 2002, since landline (non-wireless) phone use predominated. The shift to wireless communications, more minutes of use, and reliance on cell and cordless phones rather than corded phones is an extremely revealing measure of new EMF and RFR exposures for both adults and children.

The prevalence of autism has risen in parallel from one (1) in 5000 (1975) to 1 in 2500 (1985) to 1 in 500 (1995) to 1 in 250 (~2001) to 1 in 166 (~2004) to 1 in 88 (~2008) to 1 in 50 (~2013). All reflected birth cohorts born earlier<sup>1,2</sup>. Further research into autism prevalence studies have debunked the initial contention that higher numbers could be explained away by better diagnosis and broadening of diagnostic criteria<sup>3-6</sup>.

### 3.1.3. Infants, children and childbearing families are highly exposed and vulnerable

The spread of cell towers in communities, often placed on pre-school, church day-care, and school campuses, means that young children may have hundreds of thousands of times higher RFR exposures in home and school environments than existed even 20–25 years ago. In addition, the nearly universal switch to cordless and cell phones, and away from corded landline phones, means that people are experiencing close and repetitive exposures to both EMF and RFR in the home [306]. Wireless laptops and wireless internet in schools, and home offices and for homework mean even more chronic exposures to RFR, a designated IARC 2B Possible Human Carcinogen [307,308]. The great utility of handheld devices as communication aids and engaging sources of information

and satisfaction for people on the autism spectrum may come with a concerning biologically harmful underbelly.

Exposures prior to conception or during pregnancy and infancy can come from faulty wiring, proximity to power lines, or high-frequency transients from a proximate transformer on a utility pole. Sources of pulsed RFR inside the home include an electronic baby monitor in the crib, a wireless router in the next room, a DECT phone that pulses high emissions of RFR on a continuous basis 24/7, or conversion to all compact fluorescent bulbs that produce significant 'dirty electricity' for occupants due to low-kilohertz frequency fields on electrical wiring and in ambient space. Sick and vulnerable infants in neonatal intensive care units are heavily exposed from being surrounded by equipment, with negative metabolic and autonomic consequences documented [32,258].

Wireless phones and laptops exposures produce extremely low frequency pulses from the battery of the wireless device [301,306,309] and the exposures to pulsed radiofrequency microwave radiation when the wireless device is transmitting or receiving calls and emails.

Especially since EMF/RFR exposures are already classified as IARC 2B Possible Human Carcinogens, we should be actively investigating these sources of damage to DNA that could reasonably result in 'de novo mutations' but also be aware that common environmental exposures from EMF and RFR might play a role in the higher rates of concordance for autism (ASD) among twins and siblings.

Researchers also should be aware that common environmental exposures from EMF and RFR might play a role in the higher rates of autism (ASD) among twins and siblings, not solely because of maternal use of wireless devices during pregnancy and paternal sperm exposure to wireless devices peri-conception; but also because such oxidative damage to DNA can occur at levels introduced into the world of the fetus, and young developing infant and child via baby surveillance monitoring devices in the crib and wireless devices in the home. The deployment of technologies poses risks to human fertility and reproduction capacity, to the fetus, to children and adults [301].

### 3.1.4. ASC risk and genomic damage to future generations

Barouki and Grandjean make a persuasive case that public health interventions are critically needed in early childhood development to prevent adult diseases that appear decades later [310]. Although they do not include EMF or RFR but only chemicals, they do say that physiological stressors, which EMF and RFR certainly have been established, should be reduced during critical development windows. They say: "*The current pandemic of non-communicable diseases and the increased prevalence of important dysfunctions demand an open interrogation of why current interventions appear insufficient. We now know that disease risk can be induced very early in the life course and that it is modifiable by*

*nutrients and environmental chemical exposures (along with drugs, infections, and other types of stresses)” [310].*

Public health interventions are warranted now to protect the genetic heritage of humans, as well as the other stocks of genetic material in wildlife and plants in the face of what appears to be on-going impairment of these genomes. The risk of genomic damage for future generations is sufficiently documented to warrant strong preventative action and new public safety limits that observe EMF/RFR levels shown to cause adverse effects.

### 3.1.5. De-tuning the organism

Genetic mutations may lead to cancer and other diseases in the present and future generations, but the exposures that are capable of creating genotoxic impacts also compromise physiological function. Even genotoxicity can have not only specific but also non-specific effects due to molecular inefficiencies, misfolded proteins, and cellular debris [311,312].

In the setting of autism, a baby gestated or developing as a neonate in a milieu with excessively elevated EMF/RFR exposures is vulnerable to interference with the normal development processes, including the organization of information and experience in the brain. This baby's environment also often includes nutritional insufficiencies (processed denatured pesticide-laden food low in antioxidants, minerals and essential fatty acids essential to cellular protection). The baby's gestational period may have been complicated by the mother's own health issues such as conditions like obesity and diabetes [313] which converge upon on inflammation, oxidative stress and other common forms of physiological dysregulation. The exquisite 'tuning up' of the brain and body as it develops will integrate and respond to the environmental inputs it receives, and is particularly sensitive to environmental miscues (whether chemical like endocrine disruptors, EMF/RFR which can be both chemically and electromagnetically disruptive, or other environmental conditions whether hostile or nurturing). To the extent that the baby is burdened with more disorganized or hostile cues than nurturing and organizing cues, that baby may lose resiliency and become more physiologically vulnerable –perhaps approaching a tipping point into decompensation such as autistic regression or development of other chronic disease processes.

From a systems point of view, the phenomenon of 'autistic regression' can be understood as occurring after an accumulation of multisystem signaling interference leading to a tipping point of loss of some vital systems synchronization and increase in randomization. EMF/RFR exposures could plausibly contribute both to this vulnerability and to the decompensation/desynchronization process – as could other stressors such as infection, toxicity, acute stress. The vulnerability, then, is the 'allostatic load' – the total burden of stressors pressing toward disorganization. The tipping point may come in a variety of ways; but upon investigation one is likely to find that unless a stressor is severe, the trigger most proximally associated with the decompensation is likely to

be the 'straw that breaks the camel's back' laid atop a prior accumulation of 'allostatic load.'

### 3.2. Conclusions and recommendations

The case has been made that ASCs involve physiological challenges at multiple levels, and that these challenges are paralleled in the physiological impacts of EMF/RFR exposure. Evidence has also been presented to suggest that the many levels of damage and degradation of physiological and functional integrity are profoundly related to each other. Although autism spectrum conditions (ASCs) are defined by problems with behavior, communication, social interaction and sensory processing, under the surface they also involve a range of disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency radiation exposures (EMF/RFR). At the cellular and molecular level many studies of people with ASCs have identified oxidative stress and evidence of free radical damage, evidence of cellular stress proteins, as well as deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASCs can be associated with genetic mutations but more often may be downstream of inflammation or chemical exposures. Cell membrane lipids may be peroxidized, mitochondria may function poorly, and immune system disturbances of various kinds are common. Brain oxidative stress and inflammation as well as measures consistent with blood–brain barrier and brain perfusion compromise have been documented. Changes in brain and autonomic nervous system electrophysiology can be measured and seizures are far more common than in the population at large. Sleep disruption and high levels of stress are close to universal. In parallel, all of these phenomena have also been documented to result from or be modulated by EMF/RFR exposure. Moreover, some people with ASCs have de novo mutations (that their parents do not have), and EMF/RFR exposures could contribute to this due to their potential genotoxicity. EMF/RFR exposure during pregnancy may send spurious signals to developing brain cells during pregnancy, altering brain development during critical periods, and may increase oxidative stress and immune reactivity that can increase risk for later developmental impairments, with further disruption later in development increasing risk, physiological dysregulation and severity of outcome.

All of this does not prove that EMF/RFR exposures cause autism, but it does raise concerns that they could contribute by increasing risk, and by making challenging biological problems and symptoms worse in these vulnerable individuals. Placed alongside the dramatic rise in reported cases of ASCs [333], that parallels the dramatic rise in deployment of wireless technologies, a strong case can be made for aggressively investigating links between ASCs and EMR/RFR, and minimizing exposures for people with autism as well as families preconceptionally, during pregnancy, and around infants and children at home, at school, and in health care centers and hospitals.

These arguments have implications for how we understand what ASCs ‘are’ and how they work, including an appreciation that it may be the physiological disturbance is what actually generates the ‘autism’ on a moment-to-moment basis—and that these physiological disturbances are profoundly driven by environmental insults. These implications call upon us to take the environmental contribution very seriously, which involves on the one hand a sobering appreciation of the vast array of exposures that can contribute to risk via perturbed development and physiological degradation, and on the other hand a sense that there are powerful things we can do to reduce risk and improve the situation.

### 3.2.1. Change our deployment of EMF/RFR

The deployment of RFR from wireless technologies has incredible momentum, and it has made many things easier and many other things possible for the first time. On the other hand this momentum can interfere with setting up the technology in a fashion truly respectful of biological tolerances. *“There is no question that global implementation of the safety standards proposed in the Bioinitiative (2007) Report, if implemented abruptly and without careful planning, have the potential to not only be very expensive but also disruptive of life and the economy as we know it. Action must be a balance of risk to cost to benefit. The major risk from maintaining the status quo is an increasing number of cancer cases, especially in young people, as well as neurobehavioral problems at increasing frequencies. The benefits of the status quo are expansion and continued development of communication technologies. But we suspect that the true costs of even existing technologies will only become much more apparent with time. Whether the costs of remedial action are worth the societal benefits is a formula that should reward precautionary behavior”* [301].

### 3.2.2. Encourage precautions right now based on present knowledge

Physicians and health care workers should raise the visibility of EMF/RFR as a plausible environmental factor in clinical evaluations and treatment protocols. Reducing or removing EMF and wireless RFR stressors from the environment is a reasonable precautionary action given the overall weight of evidence.

- Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments,
- Special education classrooms should aim for ‘no wireless’ conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
- Adaptations to preserve the attractive design innovations of technologies such as tablet computers in a ‘no wireless’ environment should be developed.

- All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
- School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.
- Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
- There is sufficient scientific evidence to warrant the selection of wired internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later, and
- Wired classrooms should reasonably be provided to all students who opt-out of wireless environments.

Broader recommendations also apply, related to reducing the physiological vulnerability to exposures, reduce ‘allostatic load’ and build physiological resiliency through high quality nutrition, reducing exposure to toxicants and infectious agents, and reducing stress [297], all of which can be implemented safely based upon presently available knowledge.

### 3.2.3. Build an environmentally physiologically centered research program in ASCs as a platform for investigating the EMR/RFR-ASC linkage

This review has been structured around the physiological parallels between ASCs and the impacts of EMF/RFR. What is missing from the autism research agenda is some cross-study of these two bodies of research evidence. To do this we will need both a recognition of the importance of these risks, and a collaborative multi-site research program centered around a “middle-out” physiological approach [314] that can transcend the limits of the gene-brain-behavior agenda that has dominated ASC research, by incorporating this now clearly limited approach into a broader framework [315]. This still dominant gene-brain-behavior approach has been based on an expectation of linear mapping across the levels on which it focuses, but instead the systems involved appear to be much more complex. The middle-out approach is an emerging more inclusive framework in systems biology that can incorporate complexity and nonlinear, multi-scale modeling [316–320]. The physiological levels largely left out in the gene-only approach are critically important to helping people with ASCs because they will help not only with understanding how environment impacts function but also with identifying leverage points.



### 3.2.4. Take the evidence as a call to action

Both EMF and RFR exposures are already classified as IARC Group 2B Possible Human Carcinogens. The substantial scientific literature on EMF and RFR effects on DNA, on immune and blood–brain barrier disruption, on stress proteins, on circadian rhythms and hormone dysregulation, and on cognition, sleep, disruption of neural control and altered brainwave activity all argue for reduction of exposures now, and better coordinated research in these areas. The evidence is sufficiently documented to warrant strong preventative action and new public safety limits that observe EMF/RFR levels shown to cause adverse effects.

All relevant environmental conditions should be given weight in defining and implementing prudent, precautionary actions to protect public health, including EMF and RFR. Evidence is sufficient to add EMF/RFR prominently to the list of exposures that can degrade the human genome, and impair normal development, health and quality of our physiology. With the rising numbers people with ASCs and other childhood health and developmental disorders, we cannot afford to ignore this component of risk to our children and vulnerable populations. When the risk factors are largely avoidable or preventable, ignoring clear evidence of large-scale health risks to global populations poses unnecessary and unacceptable risks. Taking this evidence as a call to action will be challenging and disruptive in the short term, but constructive in the longer term as we learn to use EMF/RFR in healthier ways.

## References

- [1] K.B. Wallace, A.A. Starkov, Mitochondrial targets of drug toxicity, *Annu. Rev. Pharmacol. Toxicol.* 40 (2000) 353–388.
- [2] R. Thar, M. Kuhl, Propagation of electromagnetic radiation in mitochondria? *J. Theor. Biol.* 230 (2004) 261–270.
- [3] M.A. Aon, S. Cortassa, B. O'Rourke, Mitochondrial oscillations in physiology and pathophysiology, *Adv. Exp. Med. Biol.* 641 (2008) 98–117.
- [4] A.A. Khaki, R.S. Tubbs, M.M. Shoja, J.S. Rad, A. Khaki, R.M. Farahani, S. Zarrintan, T.C. Nag, The effects of an electromagnetic field on the boundary tissue of the seminiferous tubules of the rat: a light and transmission electron microscope study, *Folia Morphol. (Warsz)* 65 (2006) 188–194.
- [5] M.S. Lahijani, D.M. Tehrani, E. Sabouri, Histopathological and ultrastructural studies on the effects of electromagnetic fields on the liver of preincubated white Leghorn chicken embryo, *Electromagn. Biol. Med.* 28 (2009) 391–413.
- [6] M.A. Esmekaya, E. Aytekin, E. Ozgur, G. Guler, M.A. Ergun, S. Omeroglu, N. Seyhan, Mutagenic and morphologic impacts of 1.8 GHz radiofrequency radiation on human peripheral blood lymphocytes (hPBLs) and possible protective role of pre-treatment with Ginkgo biloba (EGb 761), *Sci. Total Environ.* 410–411 (2011) 59–64.
- [7] S. Xu, Z. Zhou, L. Zhang, Z. Yu, W. Zhang, Y. Wang, X. Wang, M. Li, Y. Chen, C. Chen, M. He, G. Zhang, M. Zhong, Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons, *Brain Res.* 1311 (2010) 189–196.
- [8] O.N. Chernysheva, Effect of an alternating magnetic field of industrial frequency on the lipid composition of the rat liver, *Ukr. Biokhim. Zh.* 59 (1987) 91–94.
- [9] C. Wang, J. Cong, H. Xian, X. Cao, C. Sun, K. Wu, The effects of electromagnetic pulse on fluidity and lipid peroxidation of mitochondrial membrane, *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 20 (2002) 266–268.
- [10] N. Dragicevic, P.C. Bradshaw, M. Mamcarz, X. Lin, L. Wang, C. Cao, G.W. Arendash, Long-term electromagnetic field treatment enhances brain mitochondrial function of both Alzheimer's transgenic mice and normal mice: a mechanism for electromagnetic field-induced cognitive benefit? *Neuroscience* 185 (2011) 135–149.
- [11] I. Belyaev, Evidence for Disruption by Modulation: Role of Physical and Biological Variables in Bioeffects of Non-Thermal Microwaves for Reproducibility, Cancer Risk and Safety Standards, in: C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012 <http://www.bioinitiative.org>
- [12] C. Giulivi, Y.F. Zhang, A. Omanska-Klusek, C. Ross-Inta, S. Wong, I. Hertz-Picciotto, F. Tassone, I.N. Pessah, Mitochondrial dysfunction in autism, *JAMA* 304 (2010) 2389–2396.
- [13] L. Palmieri, V. Papaleo, V. Porcelli, P. Scarcia, L. Gaita, R. Sacco, J. Hager, F. Rousseau, P. Curatolo, B. Manzi, R. Militeri, C. Bravaccio, S. Trillo, C. Schneider, R. Melmed, M. Elia, C. Lenti, M. Sacconi, T. Pascucci, S. Puglisi-Allegra, K.L. Reichelt, A.M. Persico, Altered calcium homeostasis in autism-spectrum disorders: evidence from biochemical and genetic studies of the mitochondrial aspartate/glutamate carrier AGC1, *Mol. Psychiatry* 15 (2010) 38–52.
- [14] E. Pastural, S. Ritchie, Y. Lu, W. Jin, A. Kavianpour, K. Khine Su-Myat, D. Heath, P.L. Wood, M. Fisk, D.B. Goodenowe, Novel plasma phospholipid biomarkers of autism: mitochondrial dysfunction as a putative causative mechanism, *Prostaglandins Leukot Essent. Fatty Acids* 81 (2009) 253–264.
- [15] N. Zecavati, S.J. Spence, Neurometabolic disorders and dysfunction in autism spectrum disorders, *Curr. Neurol. Neurosci. Rep.* 9 (2009) 129–136.
- [16] D.A. Rossignol, R.E. Frye, Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis, *Mol. Psychiatry* (2011) 1–25.
- [17] A. Hadjixenofontos, M.A. Schmidt, P.L. Whitehead, I. Konidari, D.J. Hedges, H.H. Wright, R.K. Abramson, R. Menon, S.M. Williams, M.L. Cuccaro, J.L. Haines, J.R. Gilbert, M.A. Pericak-Vance, E.R. Martin, J.L. McCauley, Evaluating mitochondrial DNA variation in autism spectrum disorders, *Ann. Hum. Genet.* (2012).
- [18] L. Palmieri, A.M. Persico, Mitochondrial dysfunction in autism spectrum disorders: cause or effect? *Biochim. Biophys. Acta* 1797 (2010) 1130–1137.
- [19] J. Leon, D. Acuna-Castroviejo, G. Escames, D.X. Tan, R.J. Reiter, Melatonin mitigates mitochondrial malfunction, *J. Pineal Res.* 38 (2005) 1–9.
- [20] F. Luchetti, B. Canonico, M. Betti, M. Arcangeletti, F. Pilolli, M. Piroddi, L. Canesi, S. Papa, F. Galli, Melatonin signaling and cell protection function, *FASEB J.* 24 (2010) 3603–3624.
- [21] J.H. Limon-Pacheco, M.E. Gonshebb, The glutathione system and its regulation by neurohormone melatonin in the central nervous system, *Cent. Nerv. Syst. Agents Med. Chem.* 10 (2010) 287–297.
- [22] R. Hardeland, Antioxidative protection by melatonin: multiplicity of mechanisms from radical detoxification to radical avoidance, *Endocrine* 27 (2005) 119–130.
- [23] Y.K. Gupta, M. Gupta, K. Kohli, Neuroprotective role of melatonin in oxidative stress vulnerable brain, *Indian J. Physiol. Pharmacol.* 47 (2003) 373–386.
- [24] K.K. Kesari, S. Kumar, J. Behari, 900-MHz microwave radiation promotes oxidation in rat brain, *Electromagn. Biol. Med.* 30 (2011) 219–234.
- [25] F. Oktom, F. Ozguner, H. Mollaoglu, A. Koyu, E. Uz, Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone: protection by melatonin, *Arch. Med. Res.* 36 (2005) 350–355.
- [26] K. Imaida, A. Hagiwara, H. Yoshino, S. Tamano, M. Sano, M. Futakuchi, K. Ogawa, M. Asamoto, T. Shirai, Inhibitory effects of low doses of melatonin on induction of preneoplastic liver lesions in a medium-term liver bioassay in F344 rats: relation to the

- influence of electromagnetic near field exposure, *Cancer Lett.* 155 (2000) 105–114.
- [27] H. Lai, N.P. Singh, Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells, *Bioelectromagnetics* 18 (1997) 446–454.
- [28] F. Ozguner, G. Aydin, H. Mollaoglu, O. Gokalp, A. Koyu, G. Cesur, Prevention of mobile phone induced skin tissue changes by melatonin in rat: an experimental study, *Toxicol. Ind. Health* 20 (2004) 133–139.
- [29] F. Ozguner, Y. Bardak, S. Comlekci, Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study, *Mol. Cell Biochem.* 282 (2006) 83–88.
- [30] M. Yariktas, F. Doner, F. Ozguner, O. Gokalp, H. Dogru, N. Delibas, Nitric oxide level in the nasal and sinus mucosa after exposure to electromagnetic field, *Otolaryngol. Head Neck Surg.* 132 (2005) 713–716.
- [31] D. Sokolovic, B. Djindjic, J. Nikolic, G. Bjelakovic, D. Pavlovic, G. Kocic, D. Krstic, T. Cvetkovic, V. Pavlovic, Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain, *J. Radiat. Res.* 49 (2008) 579–586.
- [32] C.V. Bellieni, M. Tei, F. Iacononi, M.L. Tataranno, S. Negro, F. Proietti, M. Longini, S. Perrone, G. Buonocore, Is newborn melatonin production influenced by magnetic fields produced by incubators? *Early Hum. Dev.* 88 (2012) 707–710.
- [33] M.S. Indredavik, T. Vik, K.A. Evensen, J. Skranes, G. Taraldsen, A.M. Brubakk, Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age, *J. Dev. Behav. Pediatr.* 31 (2010) 286–294.
- [34] M.S. Indredavik, T. Vik, J. Skranes, A.M. Brubakk, Positive screening results for autism in ex-preterm infants, *Pediatrics* 122 (2008) 222, author reply 222–223.
- [35] S. Johnson, C. Hollis, E. Hennessy, P. Kochhar, D. Wolke, N. Marlow, Screening for autism in preterm children: diagnostic utility of the social communication questionnaire, *Arch. Dis. Child* 96 (2011) 73–77.
- [36] S. Johnson, C. Hollis, P. Kochhar, E. Hennessy, D. Wolke, N. Marlow, Autism spectrum disorders in extremely preterm children, *J. Pediatr.* 156 (2010) 525–531, e522.
- [37] S. Johnson, N. Marlow, Preterm birth and childhood psychiatric disorders, *Pediatr. Res.* 69 (2011) 11R–18R.
- [38] K.M. Lampi, L. Lehtonen, P.L. Tran, A. Suominen, V. Lehti, P.N. Banerjee, M. Gissler, A.S. Brown, A. Sourander, Risk of autism spectrum disorders in low birth weight and small for gestational age infants, *J. Pediatr.* 161 (2012) 830–836.
- [39] C. Limperopoulos, Autism spectrum disorders in survivors of extreme prematurity, *Clin. Perinatol.* 36 (2009) 791–805, vi.
- [40] C. Limperopoulos, Extreme prematurity, cerebellar injury, and autism, *Semin. Pediatr. Neurol.* 17 (2010) 25–29.
- [41] C. Limperopoulos, H. Bassan, N.R. Sullivan, J.S. Soul, R.L. Robertson Jr., M. Moore, S.A. Ringer, J.J. Volpe, A.J. du Plessis, Positive screening for autism in ex-preterm infants: prevalence and risk factors, *Pediatrics* 121 (2008) 758–765.
- [42] M.L. Matson, J.L. Matson, J.S. Beighley, Comorbidity of physical and motor problems in children with autism, *Res. Dev. Disabil.* 32 (2011) 2304–2308.
- [43] J.A. Pinto-Martin, S.E. Levy, J.F. Feldman, J.M. Lorenz, N. Paneth, A.H. Whitaker, Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams, *Pediatrics* 128 (2011) 883–891.
- [44] D.A. Rossignol, R.E. Frye, Melatonin in autism spectrum disorders: a systematic review and meta-analysis, *Dev. Med. Child Neurol.* 53 (2011) 783–792.
- [45] T. Bourgeron, The possible interplay of synaptic and clock genes in autism spectrum disorders, *Cold Spring Harb. Symp. Quant. Biol.* 72 (2007) 645–654.
- [46] C. Pagan, H.G. Botros, K. Poirier, A. Dumaine, S. Jamain, S. Moreno, A. de Brouwer, H. Van Esch, R. Delorme, J.M. Launay, A. Tzschach, V. Kalscheuer, D. Lacombe, S. Briault, F. Laumonnier, M. Raynaud, B.W. van Bon, M.H. Willemsen, M. Leboyer, J. Chelly, T. Bourgeron, Mutation screening of ASMT, the last enzyme of the melatonin pathway, in a large sample of patients with intellectual disability, *BMC Med. Genet.* 12 (2011) 17.
- [47] L. Jonsson, E. Ljunggren, A. Bremer, C. Pedersen, M. Landen, K. Thuresson, M. Giacobini, J. Melke, Mutation screening of melatonin-related genes in patients with autism spectrum disorders, *BMC Med. Genet.* 3 (2010) 10.
- [48] J. Melke, H. Goubran Botros, P. Chaste, C. Betancur, G. Nygren, H. Anckarsater, M. Rastam, O. Stahlberg, I.C. Gillberg, R. Delorme, N. Chabane, M.C. Mouren-Simeoni, F. Fauchereau, C.M. Durand, F. Chevalier, X. Drouot, C. Collet, J.M. Launay, M. Leboyer, C. Gillberg, T. Bourgeron, Abnormal melatonin synthesis in autism spectrum disorders, *Mol. Psychiatry* 13 (2008) 90–98.
- [49] P. Chaste, N. Clement, O. Mercati, J.L. Guillaume, R. Delorme, H.G. Botros, C. Pagan, S. Perivier, I. Scheid, G. Nygren, H. Anckarsater, M. Rastam, O. Stahlberg, C. Gillberg, E. Serrano, N. Lemiere, J.M. Launay, M.C. Mouren-Simeoni, M. Leboyer, R. Jockers, T. Bourgeron, Identification of pathway-biased and deleterious melatonin receptor mutants in autism spectrum disorders and in the general population, *PLoS One* 5 (2010) e11495.
- [50] W. Braam, H. Keijzer, H. Struijker Boudier, R. Didden, M. Smits, L. Curfs, CYP1A2 polymorphisms in slow melatonin metabolisers: a possible relationship with autism spectrum disorder? *J. Intellect. Disabil. Res.* (2012).
- [51] D.M. Kuhn, R.E. Arthur Jr., L-DOPA-quinone inactivates tryptophan hydroxylase and converts the enzyme to a redox-cycling quinoprotein, *Brain Res. Mol. Brain Res.* 73 (1999) 78–84.
- [52] D.M. Kuhn, T.J. Geddes, Peroxynitrite inactivates tryptophan hydroxylase via sulfhydryl oxidation. Coincident nitration of enzyme tyrosyl residues has minimal impact on catalytic activity, *J. Biol. Chem.* 274 (1999) 29726–29732.
- [53] D.M. Kuhn, C.E. Sykes, T.J. Geddes, K.L. Jaunars, C. Bishop, Tryptophan hydroxylase 2 aggregates through disulfide cross-linking upon oxidation: possible link to serotonin deficits and non-motor symptoms in Parkinson's disease, *J. Neurochem.* 116 (2011) 426–437.
- [54] D.M. Kuhn, R. Arthur Jr., Molecular mechanism of the inactivation of tryptophan hydroxylase by nitric oxide: attack on critical sulfhydryls that spare the enzyme iron center, *J. Neurosci.* 17 (1997) 7245–7251.
- [55] S.D. Bilbo, J.P. Jones, W. Parker, Is autism a member of a family of diseases resulting from genetic/cultural mismatches? Implications for treatment and prevention, *Autism Res. Treat.* 2012 (2012), 910946.
- [56] A.M. Persico, J. Van de Water, C.A. Pardo, Autism: where genetics meets the immune system, *Autism Res. Treat.* 2012 (2012) 486359.
- [57] S.W. Kong, C.D. Collins, Y. Shimizu-Motohashi, I.A. Holm, M.G. Campbell, I.H. Lee, S.J. Brewster, E. Hanson, H.K. Harris, K.R. Lowe, A. Saada, A. Mora, K. Madison, R. Hundley, J. Egan, J. McCarthy, A. Eran, M. Galdzicki, L. Rappaport, L.M. Kunkel, I.S. Kohane, Characteristics and predictive value of blood transcriptome signature in males with autism spectrum disorders, *PLoS One* 7 (2012) e49475.
- [58] M.I. Waly, M. Hornig, M. Trivedi, N. Hodgson, R. Kini, A. Ohta, R. Deth, Prenatal and postnatal epigenetic programming: implications for GI, immune, and neuronal function in autism, *Autism Res. Treat.* 2012 (2012) 190930.
- [59] C. Lintas, R. Sacco, A.M. Persico, Genome-wide expression studies in autism spectrum disorder, Rett syndrome, and Down syndrome, *Neurobiol. Dis.* 45 (2012) 57–68.
- [60] P.H. Patterson, Maternal infection and immune involvement in autism, *Trends Mol. Med.* (2011).
- [61] S.E. Smith, J. Li, K. Garbett, K. Mirnics, P.H. Patterson, Maternal immune activation alters fetal brain development through interleukin-6, *J. Neurosci.* 27 (2007) 10695–10702.
- [62] E. Fox, D. Amaral, J. Van de Water, Maternal and fetal antibrain antibodies in development and disease, *Dev. Neurobiol.* 72 (2012) 1327–1334.
- [63] H. Soumiya, H. Fukumitsu, S. Furukawa, Prenatal immune challenge compromises the normal course of neurogenesis during development of the mouse cerebral cortex, *J. Neurosci. Res.* 89 (2011) 1575–1585.

- [64] L.A. Martin, P. Ashwood, D. Braunschweig, M. Cabanlit, J. Van de Water, D.G. Amaral, Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism, *Brain Behav. Immun.* 22 (2008) 806–816.
- [65] L.A. Croen, J.K. Grether, C.K. Yoshida, R. Odouli, J. Van de Water, Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study, *Arch. Pediatr. Adolesc. Med.* 159 (2005) 151–157.
- [66] S.D. Bilbo, J.M. Schwarz, The immune system and developmental programming of brain and behavior, *Front. Neuroendocrinol.* 33 (2012) 267–286.
- [67] J.M. Schwarz, S.D. Bilbo, Sex, glia, and development: interactions in health and disease, *Horm. Behav.* 62 (2012) 243–253.
- [68] P. Boksa, Effects of prenatal infection on brain development and behavior: a review of findings from animal models, *Brain Behav. Immun.* 24 (2010) 881–897.
- [69] M. Blank, Evidence for Stress Response (Stress Proteins), in: C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012, Section 7 <http://www.bioinitiative.org>
- [70] O. Johansson, Evidence for Effects on Immune Function, in: C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012, Section 8 <http://www.bioinitiative.org>
- [71] O. Johansson, Disturbance of the immune system by electromagnetic fields—a potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment, *Pathophysiology* 16 (2009) 157–177.
- [72] O. Johansson, Evidence for Effects on Immune Function, in: C. Sage, D.O. Carpenter (Eds.), *BioInitiative Report: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2007 <http://bioinitiative.org/freeaccess/report/index.htm>
- [73] A.S. Brown, E.J. Derkits, Prenatal infection and schizophrenia: a review of epidemiologic and translational studies, *Am. J. Psychiatry* 167 (2010) 261–280.
- [74] H.O. Atladottir, P. Thorsen, L. Ostergaard, D.E. Schendel, S. Lemcke, M. Abdallah, E.T. Parner, Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders, *J. Autism Dev. Disord.* 40 (2010) 1423–1430.
- [75] P.H. Patterson, Immune involvement in schizophrenia and autism: etiology, pathology and animal models, *Behav. Brain Res.* 204 (2009) 313–321.
- [76] K.A. Garbett, E.Y. Hsiao, S. Kalman, P.H. Patterson, K. Mirnics, Effects of maternal immune activation on gene expression patterns in the fetal brain, *Transl. Psychiatry* 2 (2012) e98.
- [77] D. Braunschweig, P. Duncanson, R. Boyce, R. Hansen, P. Ashwood, I.N. Pessah, I. Hertz-Picciotto, J. Van de Water, Behavioral correlates of maternal antibody status among children with autism, *J. Autism Dev. Disord.* 42 (2012) 1435–1445.
- [78] D. Braunschweig, J. Van de Water, Maternal autoantibodies in autism, *Arch. Neurol.* 69 (2012) 693–699.
- [79] P. Goines, L. Haapanen, R. Boyce, P. Duncanson, D. Braunschweig, L. Delwiche, R. Hansen, I. Hertz-Picciotto, P. Ashwood, J. Van de Water, Autoantibodies to cerebellum in children with autism associate with behavior, *Brain Behav. Immun.* 25 (2011) 514–523.
- [80] S. Wills, M. Cabanlit, J. Bennett, P. Ashwood, D.G. Amaral, J. Van de Water, Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders, *Brain Behav. Immun.* 23 (2009) 64–74.
- [81] S. Wills, C.C. Rossi, J. Bennett, V. Martinez Cerdano, P. Ashwood, D.G. Amaral, J. Van de Water, Further characterization of autoantibodies to GABAergic neurons in the central nervous system produced by a subset of children with autism, *Mol. Autism* 2 (2011) 5.
- [82] A.W. Zimmerman, S.L. Connors, K.J. Matteson, L.C. Lee, H.S. Singer, J.A. Castaneda, D.A. Pearce, Maternal antibrain antibodies in autism, *Brain Behav. Immun.* 21 (2007) 351–357.
- [83] T.S. Aldad, G. Gan, X.B. Gao, H.S. Taylor, Fetal radiofrequency radiation exposure from 800–1900 MHz-rated cellular telephones affects neurodevelopment and behavior in mice, *Sci. Rep.* 2 (2012) 312.
- [84] L. Shi, S.H. Fatemi, R.W. Sidwell, P.H. Patterson, Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring, *J. Neurosci.* 23 (2003) 297–302.
- [85] P. Ashwood, A. Enstrom, P. Krakowiak, I. Hertz-Picciotto, R.L. Hansen, L.A. Croen, S. Ozonoff, I.N. Pessah, J. Van de Water, Decreased transforming growth factor beta1 in autism: a potential link between immune dysregulation and impairment in clinical behavioral outcomes, *J. Neuroimmunol.* 204 (2008) 149–153.
- [86] P. Ashwood, P. Krakowiak, I. Hertz-Picciotto, R. Hansen, I. Pessah, J. Van de Water, Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome, *Brain Behav. Immun.* 25 (2011) 40–45.
- [87] E. Breece, B. Paciotti, C.W. Nordahl, S. Ozonoff, J.A. Van de Water, S.J. Rogers, D. Amaral, P. Ashwood, Myeloid dendritic cells frequencies are increased in children with autism spectrum disorder and associated with amygdala volume and repetitive behaviors, *Brain Behav. Immun.* (2012).
- [88] L. Heuer, P. Ashwood, J. Schauer, P. Goines, P. Krakowiak, I. Hertz-Picciotto, R. Hansen, L.A. Croen, I.N. Pessah, J. Van de Water, Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms, *Autism Res.* 1 (2008) 275–283.
- [89] M. Careaga, P. Ashwood, Autism spectrum disorders: from immunity to behavior, *Methods Mol. Biol.* 934 (2012) 219–240.
- [90] G. Broderick, T.J. Craddock, Systems biology of complex symptom profiles: capturing interactivity across behavior, brain and immune regulation, *Brain Behav. Immun.* (2012).
- [91] H. Jyonouchi, L. Geng, D.L. Streck, G.A. Toruner, Children with autism spectrum disorders (ASD) who exhibit chronic gastrointestinal (GI) symptoms and marked fluctuation of behavioral symptoms exhibit distinct innate immune abnormalities and transcriptional profiles of peripheral blood (PB) monocytes, *J. Neuroimmunol.* (2011).
- [92] M. Johansson, M. Rastam, E. Billstedt, S. Danielsson, K. Stromland, M. Miller, C. Gillberg, Autism spectrum disorders and underlying brain pathology in CHARGE association, *Dev. Med. Child Neurol.* 48 (2006) 40–50.
- [93] T.C. Theoharides, A. Angelidou, K.D. Alysandratos, B. Zhang, S. Asadi, K. Francis, E. Toniato, D. Kalogeromitros, Mast cell activation and autism, *Biochim. Biophys. Acta* 1822 (2012) 34–41.
- [94] T.C. Theoharides, A. Angelidou, K.D. Alysandratos, B. Zhang, S. Asadi, K. Francis, E. Toniato, D. Kalogeromitros, Mast cell activation and autism, *Biochim. Biophys. Acta* (2010).
- [95] B. Zhang, S. Asadi, Z. Weng, N. Sismanopoulos, T.C. Theoharides, Stimulated human mast cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions, *PLoS One* 7 (2012) e49767.
- [96] H. Seitz, D. Stinner, T. Eikmann, C. Herr, M. Roosli, Electromagnetic hypersensitivity (EHS) and subjective health complaints associated with electromagnetic fields of mobile phone communication—a literature review published between 2000 and 2004, *Sci. Total Environ.* 349 (2005) 45–55.
- [97] O. Johansson, S. Gangi, Y. Liang, K. Yoshimura, C. Jing, P.Y. Liu, Cutaneous mast cells are altered in normal healthy volunteers sitting in front of ordinary TVs/PCs—results from open-field provocation experiments, *J. Cutan. Pathol.* 28 (2001) 513–519.
- [98] B. Bakkaloglu, B. Anlar, F.Y. Anlar, F. Oktem, B. Pehlivanurk, F. Unal, C. Ozbesler, B. Gokler, Atopic features in early childhood autism, *Eur. J. Paediatr. Neurol.* 12 (2008) 476–479.
- [99] L.G. Salford, H. Nittby, B.R. Persson, Effects of EMF from wireless communication upon the blood–brain barrier, in: C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012 <http://www.bioinitiative.org>



- [100] M. Bolshakov, S. Alekseev, Bursting responses of Lymnea neurons to microwave radiation, *Bioelectromagnetics* 13 (1992) 119–129.
- [101] T.Y. Zhao, S.P. Zou, P.E. Knapp, Exposure to cell phone radiation up-regulates apoptosis genes in primary cultures of neurons and astrocytes, *Neurosci. Lett.* 412 (2007) 34–38.
- [102] P. Chan, L.F. Eng, Y.L. Lee, V.W. Lin, Effects of pulsed magnetic stimulation of GFAP levels in cultured astrocytes, *J. Neurosci. Res.* 55 (1999) 238–244.
- [103] M. Ammari, E. Brillaud, C. Gamez, A. Lecomte, M. Sakly, H. Abdelmelek, R. de Seze, Effect of a chronic GSM 900 MHz exposure on glia in the rat brain, *Biomed. Pharmacother.* 62 (2008) 273–281.
- [104] M. Ammari, C. Gamez, A. Lecomte, M. Sakly, H. Abdelmelek, R. De Seze, GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field signal, *Int. J. Radiat. Biol.* 86 (2010) 367–375.
- [105] E. Brillaud, A. Piotrowski, R. de Seze, Effect of an acute 900 MHz GSM exposure on glia in the rat brain: a time-dependent study, *Toxicology* 238 (2007) 23–33.
- [106] M.C. Ragbetli, A. Aydinlioglu, N. Koyun, C. Ragbetli, S. Bektaş, S. Ozdemir, The effect of mobile phone on the number of Purkinje cells: a stereological study, *Int. J. Radiat. Biol.* 86 (2010) 548–554.
- [107] E.N. Albert, M.F. Sherif, N.J. Papadopoulos, Effect of nonionizing radiation on the Purkinje cells of the uvula in squirrel monkey cerebellum, *Bioelectromagnetics* 2 (1981) 241–246.
- [108] E.N. Albert, M.F. Sherif, N.J. Papadopoulos, F.J. Slaby, J. Monahan, Effect of nonionizing radiation on the Purkinje cells of the rat cerebellum, *Bioelectromagnetics* 2 (1981) 247–257.
- [109] X. Yang, G. He, Y. Hao, C. Chen, M. Li, Y. Wang, G. Zhang, Z. Yu, The role of the JAK2-STAT3 pathway in pro-inflammatory responses of EMF-stimulated N9 microglial cells, *J. Neuroinflammation* 7 (2010) 54.
- [110] D.G. Amaral, C.M. Schumann, C.W. Nordahl, Neuroanatomy of autism, *Trends Neurosci.* 31 (2008) 137–145.
- [111] P. Levitt, D.B. Campbell, The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders, *J. Clin. Invest.* 119 (2009) 747–754.
- [112] D.H. Geschwind, P. Levitt, Autism spectrum disorders: developmental disconnection syndromes, *Curr. Opin. Neurobiol.* 17 (2007) 103–111.
- [113] R. Anney, L. Klei, D. Pinto, R. Regan, J. Conroy, T.R. Magalhaes, C. Correia, B.S. Abrahams, N. Sykes, A.T. Pagnamenta, J. Almeida, E. Bacchelli, A.J. Bailey, G. Baird, A. Battaglia, T. Berney, N. Bolshakova, S. Bolte, P.F. Bolton, T. Bourgeron, S. Brennan, J. Brian, A.R. Carson, G. Casallo, J. Casey, S.H. Chu, L. Cochrane, C. Corsello, E.L. Crawford, A. Crossett, G. Dawson, M. de Jonge, R. Delorme, I. Drmic, E. Duketis, F. Duque, A. Estes, P. Farrar, B.A. Fernandez, S.E. Folstein, E. Fombonne, C.M. Freitag, J. Gilbert, C. Gillberg, J.T. Glessner, J. Goldberg, J. Green, S.J. Guter, H. Hakonarson, E.A. Heron, M. Hill, R. Holt, J.L. Howe, G. Hughes, V. Hus, R. Iglizzi, C. Kim, S.M. Klauck, A. Kolevzon, O. Korvatska, V. Kustanovich, C.M. Lajonchere, J.A. Lamb, M. Laskawiec, M. Leboyer, A. Le Couteur, B.L. Leventhal, A.C. Lionel, X.Q. Liu, C. Lord, L. Lotspeich, S.C. Lund, E. Maestrini, W. Mahoney, C. Mantoulan, C.R. Marshall, H. McConachie, C.J. McDougle, J. McGrath, W.M. McMahon, N.M. Melhem, A. Merikangas, O. Migita, N.J. Minshew, G.K. Mirza, J. Munson, S.F. Nelson, C. Noakes, A. Noor, G. Nygren, G. Oliveira, K. Papanikolaou, J.R. Parr, B. Parrini, T. Paton, A. Pickles, J. Piven, D.J. Posey, A. Poustka, F. Poustka, A. Prasad, J. Ragoussis, K. Renshaw, J. Rickaby, W. Roberts, K. Roeder, B. Roge, M.L. Rutter, L.J. Bierut, J.P. Rice, J. Salt, K. Sansom, D. Sato, R. Segurado, L. Senman, N. Shah, V.C. Sheffield, L. Soorya, I. Sousa, V. Stoppioni, C. Strawbridge, R. Tancredi, K. Tansey, B. Thiruvahindrapuram, A.P. Thompson, S. Thomson, A. Tryfon, J. Tsiantis, H. Van Engeland, J.B. Vincent, F. Volkmar, S. Wallace, K. Wang, Z. Wang, T.H. Wassink, K. Wing, K. Wittemeyer, S. Wood, B.L. Yaspan, D. Zurawiecki, L. Zwaigenbaum, C. Betancur, J.D. Buxbaum, R.M. Cantor, E.H. Cook, H. Coon, M.L. Cuccaro, L. Gallagher, D.H. Geschwind, M. Gill, J.L. Haines, J. Miller, A.P. Monaco, J.I. Nurnberger Jr., A.D. Paterson, M.A. Pericak-Vance, G.D. Schellenberg, S.W. Scherer, J.S. Sutcliffe, P. Szatmari, A.M. Vicente, V.J. Vieland, E.M. Wijsman, B. Devlin, S. Ennis, J. Hallmayer, A genome-wide scan for common alleles affecting risk for autism, *Hum. Mol. Genet.* 19 (2010) 4072–4082.
- [114] M.F. Casanova, Neuropathological and genetic findings in autism: the significance of a putative minicolumnopathy, *Neuroscientist* 12 (2006) 435–441.
- [115] J.L. Rubenstein, M.M. Merzenich, Model of autism: increased ratio of excitation/inhibition in key neural systems, *Gene. Brain Behav.* 2 (2003) 255–267.
- [116] M.R. Herbert, The neuroanatomy of autism, in: D.A. Fein (Ed.), *The Neuropsychology of Autism*, Oxford University Press, New York, NY, 2011, pp. 47–76.
- [117] M.L. Bauman, T.L. Kemper, Neuroanatomic observations of the brain in autism: a review and future directions, *Int. J. Dev. Neurosci.* 23 (2005) 183–187.
- [118] M.R. Herbert, Large brains in autism: the challenge of pervasive abnormality, *Neuroscientist* 11 (2005) 417–440.
- [119] J.A. Laurence, S.H. Fatemi, Glial fibrillary acidic protein is elevated in superior frontal, parietal and cerebellar cortices of autistic subjects, *Cerebellum* 4 (2005) 206–210.
- [120] V.K. Singh, R. Warren, R. Averett, M. Ghaziuddin, Circulating autoantibodies to neuronal and glial filament proteins in autism, *Pediatr. Neurol.* 17 (1997) 88–90.
- [121] S.H. Fatemi, T.D. Folsom, T.J. Reutiman, S. Lee, Expression of astrocytic markers aquaporin 4 and connexin 43 is altered in brains of subjects with autism, *Synapse* 62 (2008) 501–507.
- [122] D.L. Vargas, C. Nascimbene, C. Krishnan, A.W. Zimmerman, C.A. Pardo, Neuroglial activation and neuroinflammation in the brain of patients with autism, *Ann. Neurol.* 57 (2005) 67–81.
- [123] N.A. Tetreault, A.Y. Hakeem, S. Jiang, B.A. Williams, E. Allman, B.J. Wold, J.M. Allman, Microglia in the cerebral cortex in autism, *J. Autism Dev. Disord.* 42 (2012) 2569–2584.
- [124] J.T. Morgan, G. Chana, I. Abramson, K. Semendeferi, E. Courchesne, I.P. Everall, Abnormal microglial-neuronal spatial organization in the dorsolateral prefrontal cortex in autism, *Brain Res.* 1456 (2012) 72–81.
- [125] K. Suzuki, G. Sugihara, Y. Ouchi, K. Nakamura, M. Futatsubashi, Microglial activation in young adults with Autism spectrum disorder, *JAMA Psychiatry* 70 (2013) 49–58.
- [126] K. Garbett, P.J. Ebert, A. Mitchell, C. Lintas, B. Manzi, K. Mirnics, A.M. Persico, Immune transcriptome alterations in the temporal cortex of subjects with autism, *Neurobiol. Dis.* 30 (2008) 303–311.
- [127] I. Voineagu, X. Wang, P. Johnston, J.K. Lowe, Y. Tian, S. Horvath, J. Mill, R.M. Cantor, B.J. Blencowe, D.H. Geschwind, Transcriptomic analysis of autistic brain reveals convergent molecular pathology, *Nature* 474 (2011) 380–384.
- [128] S. Baron-Cohen, H.A. Ring, E.T. Bullmore, S. Wheelwright, C. Ashwin, S.C. Williams, The amygdala theory of autism, *Neurosci. Biobehav. Rev.* 24 (2000) 355–364.
- [129] I. Dziobek, M. Bahnemann, A. Convit, H.R. Heekeren, The role of the fusiform-amygdala system in the pathophysiology of autism, *Arch. Gen. Psychiatry* 67 (2010) 397–405.
- [130] G.B. Hall, K.A. Doyle, J. Goldberg, D. West, P. Szatmari, Amygdala engagement in response to subthreshold presentations of anxious face stimuli in adults with autism spectrum disorders: preliminary insights, *PLoS One* 5 (2010) e10804.
- [131] M.T. Mercadante, R.M. Cysneiros, J.S. Schwartzman, R.M. Arida, E.A. Cavalheiro, F.A. Scorza, Neurogenesis in the amygdala: a new etiologic hypothesis of autism? *Med. Hypotheses* 70 (2008) 352–357.

- [132] C.W. Nordahl, R. Scholz, X. Yang, M.H. Buonocore, T. Simon, S. Rogers, D.G. Amaral, Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study, *Arch. Gen. Psychiatry*. 69 (2012) 53–61.
- [133] H. Otsuka, M. Harada, K. Mori, S. Hisaoka, H. Nishitani, Brain metabolites in the hippocampus–amygdala region and cerebellum in autism: an 1H-MR spectroscopy study, *Neuroradiology* 41 (1999) 517–519.
- [134] J. Schulkin, Autism and the amygdala: an endocrine hypothesis, *Brain Cogn.* 65 (2007) 87–99.
- [135] C.M. Schumann, D.G. Amaral, Stereological analysis of amygdala neuron number in autism, *J. Neurosci.* 26 (2006) 7674–7679.
- [136] C.M. Schumann, C.C. Barnes, C. Lord, E. Courchesne, Amygdala enlargement in toddlers with autism related to severity of social and communication impairments, *Biol. Psychiatry*. 66 (2009) 942–949.
- [137] W.A. Truitt, T.J. Sajdyk, A.D. Dietrich, B. Oberlin, C.J. McDougale, A. Shekhar, From anxiety to autism: spectrum of abnormal social behaviors modeled by progressive disruption of inhibitory neuronal function in the basolateral amygdala in Wistar rats, *Psychopharmacology (Berl)* 191 (2007) 107–118.
- [138] M. Zirlinger, D. Anderson, Molecular dissection of the amygdala and its relevance to autism, *Gene. Brain Behav.* 2 (2003) 282–294.
- [139] R.T. Johnson, S.M. Breedlove, C.L. Jordan, Astrocytes in the amygdala, *Vitam. Horm.* 82 (2010) 23–45.
- [140] A. Anitha, K. Nakamura, I. Thanseem, H. Matsuzaki, T. Miyachi, M. Tsujii, Y. Iwata, K. Suzuki, T. Sugiyama, N. Mori, Downregulation of the expression of mitochondrial electron transport complex genes in autism brains, *Brain Pathol.* (2012).
- [141] A. Chauhan, F. Gu, M.M. Essa, J. Wegiel, K. Kaur, W. Ted Brown, V. Chauhan, Brain region-specific deficit in mitochondrial electron transport chain complexes in children with autism, *J. Neurochem.* (2011).
- [142] A. Chauhan, T. Audhya, V. Chauhan, Brain region-specific glutathione redox imbalance in autism, *Neurochem. Res.* 37 (2012) 1681–1689.
- [143] S. Rose, S. Melnyk, O. Pavliv, S. Bai, T.G. Nick, R.E. Frye, S.J. James, Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain, *Transl. Psychiatry*. 2 (2012) e134.
- [144] E.M. Sajdel-Sulkowska, M. Xu, N. Koibuchi, Increase in cerebellar neurotrophin-3 and oxidative stress markers in autism, *Cerebellum* 8 (2009) 366–372.
- [145] E.R. Whitney, T.L. Kemper, D.L. Rosene, M.L. Bauman, G.J. Blatt, Density of cerebellar basket and stellate cells in autism: evidence for a late developmental loss of Purkinje cells, *J. Neurosci. Res.* 87 (2009) 2245–2254.
- [146] E.R. Whitney, T.L. Kemper, M.L. Bauman, D.L. Rosene, G.J. Blatt, Cerebellar Purkinje cells are reduced in a subpopulation of autistic brains: a stereological experiment using calbindin-D28k, *Cerebellum* 7 (2008) 406–416.
- [147] L. Shi, S.E. Smith, N. Malkova, D. Tse, Y. Su, P.H. Patterson, Activation of the maternal immune system alters cerebellar development in the offspring, *Brain Behav. Immun.* 23 (2009) 116–123.
- [148] G.J. Blatt, S.H. Fatemi, Alterations in GABAergic biomarkers in the autism brain: research findings and clinical implications, *Anat. Rec. (Hoboken)* 294 (2011) 1646–1652.
- [149] S.H. Fatemi, A.R. Halt, G. Realmuto, J. Earle, D.A. Kist, P. Thuras, A. Merz, Purkinje cell size is reduced in cerebellum of patients with autism, *Cell Mol. Neurobiol.* 22 (2002) 171–175.
- [150] S.H. Fatemi, K.A. Aldinger, P. Ashwood, M.L. Bauman, C.D. Blaha, G.J. Blatt, A. Chauhan, V. Chauhan, S.R. Dager, P.E. Dickson, A.M. Estes, D. Goldowitz, D.H. Heck, T.L. Kemper, B.H. King, L.A. Martin, K.J. Millen, G. Mittleman, M.W. Mosconi, A.M. Persico, J.A. Sweeney, S.J. Webb, J.P. Welsh, Consensus paper: pathological role of the cerebellum in autism, *Cerebellum* (2012).
- [151] J. Yip, J.J. Soghomonian, G.J. Blatt, Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications, *Acta Neuropathol.* 113 (2007) 559–568.
- [152] J. Yip, J.J. Soghomonian, G.J. Blatt, Increased GAD67 mRNA expression in cerebellar interneurons in autism: implications for Purkinje cell dysfunction, *J. Neurosci. Res.* 86 (2008) 525–530.
- [153] J. Yip, J.J. Soghomonian, G.J. Blatt, Decreased GAD65 mRNA levels in select subpopulations of neurons in the cerebellar dentate nuclei in autism: an in situ hybridization study, *Autism Res.* 2 (2009) 50–59.
- [154] S.R. Dager, S.D. Friedman, H. Petropoulos, D.W.W. Shaw, *Imaging Evidence for Pathological Brain Development in Autism Spectrum Disorders*, Humana Press, Totowa, NJ, 2008.
- [155] M.K. Bode, M.L. Mattila, V. Kiviniemi, J. Rahko, I. Moilanen, H. Ebeling, O. Tervonen, J. Nikkinen, White matter in autism spectrum disorders—evidence of impaired fiber formation, *Acta Radiol.* 52 (2011) 1169–1174.
- [156] C. Cascio, M. Gribbin, S. Gouttard, R.G. Smith, M. Jomier, S. Field, M. Graves, H.C. Hazlett, K. Muller, G. Gerig, J. Piven, Fractional anisotropy distributions in 2- to 6-year-old children with autism, *J. Intellect. Disabil. Res.* (2012).
- [157] K.M. Mak-Fan, D. Morris, J. Vidal, E. Anagnostou, W. Roberts, M.J. Taylor, White matter and development in children with an autism spectrum disorder, *Autism* (2012).
- [158] B.G. Travers, N. Adluru, C. Ennis, P.M. Tromp do, D. Destiche, S. Doran, E.D. Bigler, N. Lange, J.E. Lainhart, A.L. Alexander, Diffusion tensor imaging in autism spectrum disorder: a review, *Autism Res.* 5 (2012) 289–313.
- [159] L. Walker, M. Gozzi, R. Lenroot, A. Thurm, B. Behseta, S. Swedo, C. Pierpaoli, Diffusion tensor imaging in young children with autism: biological effects and potential confounds, *Biol. Psychiatry*. 72 (2012) 1043–1051.
- [160] J.J. Wolff, H. Gu, G. Gerig, J.T. Ellison, M. Styner, S. Gouttard, K.N. Botteron, S.R. Dager, G. Dawson, A.M. Estes, A.C. Evans, H.C. Hazlett, P. Kostopoulos, R.C. McKinstry, S.J. Paterson, R.T. Schultz, L. Zwaigenbaum, J. Piven, Differences in white matter fiber tract development present from 6 to 24 months in infants with autism, *Am. J. Psychiatry*. 169 (2012) 589–600.
- [161] S.K. Sundaram, A. Kumar, M.I. Makki, M.E. Behen, H.T. Chugani, D.C. Chugani, Diffusion tensor imaging of frontal lobe in autism spectrum disorder, *Cereb. Cortex*. 18 (2008) 2659–2665.
- [162] M.R. Herbert, Why aren't we there yet? Valuable but incomplete measures of brain changes in babies with autism, *Autism Why and How*, 2012.
- [163] R.A. Muller, N. Kleinhaus, N. Kemmotsu, K. Pierce, E. Courchesne, Abnormal variability and distribution of functional maps in autism: an fMRI study of visuomotor learning, *Am. J. Psychiatry*. 160 (2003) 1847–1862.
- [164] I. Dinstein, D.J. Heeger, L. Lorenzi, N.J. Minshew, R. Malach, M. Behrmann, Unreliable evoked responses in autism, *Neuron* 75 (2012) 981–991.
- [165] S. Carrubba, A.A. Marino, The effects of low-frequency environmental-strength electromagnetic fields on brain electrical activity: a critical review of the literature, *Electromagn. Biol. Med.* 27 (2008) 83–101.
- [166] A.A. Marino, R.M. Wolcott, R. Chervenak, F. Jourdeuil, E. Nilsen, C. Frilot 2nd, S.B. Pruett, Coincident nonlinear changes in the endocrine and immune systems due to low-frequency magnetic fields, *Neuroimmunomodulation* 9 (2001) 65–77.
- [167] A.A. Marino, C. Frilot Jr., Comment on “proposed test for detection of nonlinear responses in biological preparations exposed to RF energy”, *Bioelectromagnetics* 24 (2003) 70–72, discussion 73.
- [168] S. Carrubba, C. Frilot, A. Chesson, A.A. Marino, Detection of nonlinear event-related potentials, *J. Neurosci. Methods* 157 (2006) 39–47.
- [169] S. Carrubba, A. Minagar, A.L. Chesson Jr., C. Frilot 2nd, A.A. Marino, Increased determinism in brain electrical activity occurs in association with multiple sclerosis, *Neurol. Res.* 34 (2012) 286–290.



- [170] A.A. Marino, E. Nilsen, C. Frilot, Nonlinear changes in brain electrical activity due to cell phone radiation, *Bioelectromagnetics* 24 (2003) 339–346.
- [171] A.A. Marino, R.M. Wolcott, R. Chervenak, F. Jourdeuil, E. Nilsen, C. Frilot 2nd, Nonlinear determinism in the immune system. In vivo influence of electromagnetic fields on different functions of murine lymphocyte subpopulations, *Immunol. Invest.* 30 (2001) 313–334.
- [172] A.A. Marino, R.M. Wolcott, R. Chervenak, F. Jourdeuil, E. Nilsen, C. Frilot 2nd, Nonlinear dynamical law governs magnetic field induced changes in lymphoid phenotype, *Bioelectromagnetics* 22 (2001) 529–546.
- [173] S. Carrubba, C. Frilot, A.L. Chesson, A.A. Marino, Nonlinear EEG activation evoked by low-strength low-frequency magnetic fields, *Neurosci. Lett.* 417 (2007) 212–216.
- [174] A.A. Marino, R.M. Wolcott, R. Chervenak, F. Jourdeuil, E. Nilsen, C. Frilot 2nd, Nonlinear response of the immune system to power-frequency magnetic fields, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279 (2000) R761–R768.
- [175] M. Bachmann, J. Kalda, J. Lass, V. Tuulik, M. Sakki, H. Hinrikus, Non-linear analysis of the electroencephalogram for detecting effects of low-level electromagnetic fields, *Med. Biol. Eng. Comput.* 43 (2005) 142–149.
- [176] S. Kuhn, U. Lott, A. Kramer, N. Kuster, Assessment of Human Exposure to Electromagnetic Radiation from Wireless Devices in Home and Office Environments, 2012 [http://www.who.int/peh-emf/meetings/archive/bsw\\_kuster.pdf](http://www.who.int/peh-emf/meetings/archive/bsw_kuster.pdf)
- [177] C.V. Bellieni, I. Pinto, A. Bogi, N. Zoppetti, D. Andreuccetti, G. Buonocore, Exposure to electromagnetic fields from laptop use of “laptop” computers, *Arch. Environ. Occup. Health* 67 (2012) 31–36.
- [178] J. Theberge, Perfusion magnetic resonance imaging in psychiatry, *Top. Magn. Reson. Imaging* 19 (2008) 111–130.
- [179] M.S. George, D.C. Costa, K. Kouris, H.A. Ring, P.J. Ell, Cerebral blood flow abnormalities in adults with infantile autism, *J. Nerv. Ment. Dis.* 180 (1992) 413–417.
- [180] S. Gupta, B. Ratnam, Cerebral perfusion abnormalities in children with autism and mental retardation a segmental quantitative SPECT Study, *Indian Pediatr.* 46 (2009) 161–164.
- [181] B. Degirmenci, S. Miral, G.C. Kaya, L. Iyilikci, G. Arslan, A. Baykara, I. Evren, H. Durak, Technetium-99m HMPAO brain SPECT in autistic children and their families, *Psychiatry. Res.* 162 (2008) 236–243.
- [182] J. Wilcox, M.T. Tsuang, E. Ledger, J. Algeo, T. Schnurr, Brain perfusion in autism varies with age, *Neuropsychobiology* 46 (2002) 13–16.
- [183] L. Galuska, S.J. Szakall, M. Emri, R. Olah, J. Varga, I. Garai, J. Kollar, I. Pataki, L. Tron, PET and SPECT scans in autistic children, *Orv. Hetil.* 143 (2002) 1302–1304.
- [184] T. Ohnishi, H. Matsuda, T. Hashimoto, T. Kunihiro, M. Nishikawa, T. Uema, M. Sasaki, Abnormal regional cerebral blood flow in childhood autism, *Brain* 123 (Pt 9) (2000) 1838–1844.
- [185] N. Boddaert, N. Chabane, C. Barthelemy, M. Bourgeois, J.B. Poline, F. Brunelle, Y. Samson, M. Zilbovicius, Bitemporal lobe dysfunction in infantile autism: positron emission tomography study, *J. Radiol.* 83 (2002) 1829–1833.
- [186] L. Burroni, A. Orsi, L. Monti, Y. Hayek, R. Rocchi, A.G. Vattimo, Regional cerebral blood flow in childhood autism: a SPET study with SPM evaluation, *Nucl. Med. Commun.* 29 (2008) 150–156.
- [187] T. Hashimoto, M. Sasaki, M. Fukumizu, S. Hanaoka, K. Sugai, H. Matsuda, Single-photon emission computed tomography of the brain in autism: effect of the developmental level, *Pediatr. Neurol.* 23 (2000) 416–420.
- [188] Y.H. Ryu, J.D. Lee, P.H. Yoon, D.I. Kim, H.B. Lee, Y.J. Shin, Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: comparison with findings on magnetic resonance imaging, *Eur. J. Nucl. Med.* 26 (1999) 253–259.
- [189] S.E. Starkstein, S. Vazquez, D. Vrancic, V. Nanclares, F. Manes, J. Piven, C. Plebst, SPECT findings in mentally retarded autistic individuals, *J. Neuropsychiatry. Clin. Neurosci.* 12 (2000) 370–375.
- [190] M. Zilbovicius, N. Boddaert, P. Belin, J.B. Poline, P. Remy, J.F. Mangin, L. Thivard, C. Barthelemy, Y. Samson, Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography, *Am. J. Psychiatry.* 157 (2000) 1988–1993.
- [191] H. Ito, K. Mori, T. Hashimoto, M. Miyazaki, A. Hori, S. Kagami, Y. Kuroda, Findings of brain 99mTc-ECD SPECT in high-functioning autism—3-dimensional stereotactic ROI template analysis of brain SPECT, *J. Med. Invest.* 52 (2005) 49–56.
- [192] N.D. Volkow, D. Tomasi, G.J. Wang, P. Vaska, J.S. Fowler, F. Telang, D. Alexoff, J. Logan, C. Wong, Effects of cell phone radiofrequency signal exposure on brain glucose metabolism, *JAMA* 305 (2011) 808–813.
- [193] M.S. Kwon, V. Vorobyev, S. Kannala, M. Laine, J.O. Rinne, T. Toivonen, J. Johansson, M. Teras, H. Lindholm, T. Alanko, H. Hamalainen, GSM mobile phone radiation suppresses brain glucose metabolism, *J. Cereb. Blood Flow Metab.* 31 (2011) 2293–2301.
- [194] J.G. Tasker, S.H. Olie, J.S. Bains, C.H. Brown, J.E. Stern, Glial regulation of neuronal function: from synapse to systems physiology, *J. Neuroendocrinol.* 24 (2012) 566–576.
- [195] C. Eroglu, B.A. Barres, Regulation of synaptic connectivity by glia, *Nature* 468 (2010) 223–231.
- [196] S.D. Bilbo, J.M. Schwarz, Early-life programming of later-life brain and behavior: a critical role for the immune system, *Front. Behav. Neurosci.* 3 (2009) 14.
- [197] R.D. Fields, Advances in understanding neuron-glia interactions, *Neuron. Glia. Biol.* 2 (2006) 23–26.
- [198] O. Pascual, S. Ben Achour, P. Rostaing, A. Triller, A. Bessis, Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission, *PNAS* 109 (2012) E197–E205.
- [199] K.M. Rodgers, M.R. Hutchinson, A. Northcutt, S.F. Maier, L.R. Watkins, D.S. Barth, The cortical innate immune response increases local neuronal excitability leading to seizures, *Brain* 132 (2009) 2478–2486.
- [200] F. Gardoni, M. Boraso, E. Zianni, E. Corsini, C.L. Galli, F. Cattabeni, M. Marinovich, M. Di Luca, B. Viviani, Distribution of interleukin-1 receptor complex at the synaptic membrane driven by interleukin-1beta and NMDA stimulation, *J. Neuroinflammation* 8 (2011) 14.
- [201] A. Vezzani, J. French, T. Bartfai, T.Z. Baram, The role of inflammation in epilepsy, *Nat. Rev. Neurol.* 7 (2011) 31–40.
- [202] A. Mihaly, B. Bozoky, Immunohistochemical localization of extravasated serum albumin in the hippocampus of human subjects with partial and generalized epilepsies and epileptiform convulsions, *Acta Neuropathol.* 65 (1984) 25–34.
- [203] L. Librizzi, F. Noe, A. Vezzani, M. de Curtis, T. Ravizza, Seizure-induced brain-borne inflammation sustains seizure recurrence and blood–brain barrier damage, *Ann. Neurol.* 72 (2012) 82–90.
- [204] N. Marchi, Q. Teng, C. Ghosh, Q. Fan, M.T. Nguyen, N.K. Desai, H. Bawa, P. Rasmussen, T.K. Masaryk, D. Janigro, Blood–brain barrier damage, but not parenchymal white blood cells, is a hallmark of seizure activity, *Brain Res.* 1353 (2010) 176–186.
- [205] E.A. van Vliet, S. da Costa Araujo, S. Redeker, R. van Schaik, E. Aronica, J.A. Gorter, Blood–brain barrier leakage may lead to progression of temporal lobe epilepsy, *Brain* 130 (2007) 521–534.
- [206] E. Yan, M. Castillo-Melendez, G. Smythe, D. Walker, Quinolinic acid promotes albumin deposition in Purkinje cell, astrocytic activation and lipid peroxidation in fetal brain, *Neuroscience* 134 (2005) 867–875.
- [207] F. Tore, P. Dulou, E. Haro, B. Veyret, P. Aubineau, Effect of 2 h GSM-900 microwave exposures at 2.0, 0.5 and 0.12 W/kg on plasma protein extravasation in rat brain and dura mater, *Proceedings of the 24th Annual Meeting of the BEMS2002*, 2002.
- [208] F. Tore, P. Dulou, E. Hoar, B. Veyret, P. Aubineau, Two-hour exposure to 2-W/kg, 900-MHz GSM microwaves induces plasma protein

- extravasation in rat brain and dura mater, Proceedings of the fifth International congress of the EBFA, Helsinki, Finland, 2001.
- [209] F. Vecchio, M. Tombini, P. Buffo, G. Assenza, G. Pellegrino, A. Benvenega, C. Babiloni, P.M. Rossini, Mobile phone emission increases inter-hemispheric functional coupling of electroencephalographic alpha rhythms in epileptic patients, *Int. J. Psychophysiol.* 84 (2012) 164–171.
  - [210] M. Tombini, G. Pellegrino, P. Pasqualetti, G. Assenza, A. Benvenega, E. Fabrizio, P.M. Rossini, Mobile phone emissions modulate brain excitability in patients with focal epilepsy, *Brain Stimul.* (2012).
  - [211] M. Carballo-Quintas, I. Martinez-Silva, C. Cadarso-Suarez, M. Alvarez-Figueiras, F.J. Ares-Pena, E. Lopez-Martin, A study of neurotoxic biomarkers, c-fos and GFAP after acute exposure to GSM radiation at 900 MHz in the picrotoxin model of rat brains, *Neurotoxicology* 32 (2011) 478–494.
  - [212] P. Varro, R. Szemerszky, G. Bardos, I. Vilagi, Changes in synaptic efficacy and seizure susceptibility in rat brain slices following extremely low-frequency electromagnetic field exposure, *Bioelectromagnetics* 30 (2009) 631–640.
  - [213] L.S. St-Pierre, G.H. Parker, G.A. Bubenik, M.A. Persinger, Enhanced mortality of rat pups following inductions of epileptic seizures after perinatal exposures to 5 nT, 7 Hz magnetic fields, *Life Sci.* 81 (2007) 1496–1500.
  - [214] A.W. Buckley, A.J. Rodriguez, K. Jennison, J. Buckley, A. Thurm, S. Sato, S. Swedo, Rapid eye movement sleep percentage in children with autism compared with children with developmental delay and typical development, *Arch. Pediatr. Adolesc. Med.* 164 (2010) 1032–1037.
  - [215] F. Giannotti, F. Cortesi, A. Cerquiglini, C. Vagnoni, D. Valente, Sleep in children with autism with and without autistic regression, *J. Sleep Res.* 20 (2011) 338–347.
  - [216] A.A. Borbely, R. Huber, T. Graf, B. Fuchs, E. Gallmann, P. Achermann, Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram, *Neurosci. Lett.* 275 (1999) 207–210.
  - [217] R. Huber, J. Schuderer, T. Graf, K. Jutz, A.A. Borbely, N. Kuster, P. Achermann, Radio frequency electromagnetic field exposure in humans: estimation of SAR distribution in the brain, effects on sleep and heart rate, *Bioelectromagnetics* 24 (2003) 262–276.
  - [218] J.M. Clinton, C.J. Davis, M.R. Zielinski, K.A. Jewett, J.M. Krueger, Biochemical regulation of sleep and sleep biomarkers, *J. Clin. Sleep Med.* 7 (2011) S38–S42.
  - [219] L. Sun, C. Grutzner, S. Bolte, M. Wibrall, T. Tozman, S. Schlitt, F. Poustka, W. Singer, C.M. Freitag, P.J. Uhlhaas, Impaired gamma-band activity during perceptual organization in adults with autism spectrum disorders: evidence for dysfunctional network activity in frontal-posterior cortices, *J. Neurosci.* 32 (2012) 9563–9573.
  - [220] D.C. Rojas, K. Maharajh, P. Teale, S.J. Rogers, Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism, *BMC Psychiatry.* 8 (2008) 66.
  - [221] G. Rippon, J. Brock, C. Brown, J. Boucher, Disordered connectivity in the autistic brain: challenges for the “new psychophysiology”, *Int. J. Psychophysiol.* 63 (2007) 164–172.
  - [222] A.L. Tierney, L. Gabard-Durnam, V. Vogel-Farley, H. Tager-Flusberg, C.A. Nelson, Developmental trajectories of resting EEG power: an endophenotype of autism spectrum disorder, *PLoS One* 7 (2012) e39127.
  - [223] E.V. Orekhova, T.A. Stroganova, G. Nygren, M.M. Tsetlin, I.N. Posikera, C. Gillberg, M. Elam, Excess of high frequency electroencephalogram oscillations in boys with autism, *Biol. Psychiatry.* 62 (2007) 1022–1029.
  - [224] R.A. Muller, From loci to networks and back again: anomalies in the study of autism, *Ann. N. Y. Acad. Sci.* 1145 (2008) 300–315.
  - [225] R.A. Muller, P. Shih, B. Keehn, J.R. Deyoe, K.M. Leyden, D.K. Shukla, Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders, *Cereb. Cortex.* 21 (2011) 2233–2243.
  - [226] S. Wass, Distortions and disconnections: disrupted brain connectivity in autism, *Brain Cogn.* 75 (2011) 18–28.
  - [227] M.A. Just, V.L. Cherkassky, T.A. Keller, N.J. Minshew, Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity, *Brain* 127 (2004) 1811–1821.
  - [228] F.H. Duffy, H. Als, A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls—a large case control study, *BMC Med.* 10 (2012) 64.
  - [229] J.R. Isler, K.M. Martien, P.G. Grieve, R.I. Stark, M.R. Herbert, Reduced functional connectivity in visual evoked potentials in children with autism spectrum disorder, *Clin. Neurophysiol.* (2010).
  - [230] M. Murias, J.M. Swanson, R. Srinivasan, Functional connectivity of frontal cortex in healthy and ADHD children reflected in EEG coherence, *Cereb. Cortex.* 17 (2007) 1788–1799.
  - [231] M. Murias, S.J. Webb, J. Greenson, G. Dawson, Resting state cortical connectivity reflected in EEG coherence in individuals with autism, *Biol. Psychiatry.* 62 (2007) 270–273.
  - [232] R. Coben, A.R. Clarke, W. Hudspeth, R.J. Barry, EEG power and coherence in autistic spectrum disorder, *Clin. Neurophysiol.* 119 (2008) 1002–1009.
  - [233] M.C. Lai, M.V. Lombardo, B. Chakrabarti, S.A. Sadek, G. Pasco, S.J. Wheelwright, E.T. Bullmore, S. Baron-Cohen, J. Suckling, A shift to randomness of brain oscillations in people with autism, *Biol. Psychiatry.* 68 (2010) 1092–1099.
  - [234] A. Catarino, O. Churches, S. Baron-Cohen, A. Andrade, H. Ring, Atypical EEG complexity in autism spectrum conditions: a multiscale entropy analysis, *Clin. Neurophysiol.* 122 (2011) 2375–2383.
  - [235] K.J. Mathewson, M.K. Jetha, I.E. Drmic, S.E. Bryson, J.O. Goldberg, L.A. Schmidt, Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder, *Clin. Neurophysiol.* 123 (2012) 1798–1809.
  - [236] M. Ahmadlou, H. Adeli, A. Adeli, Fractality and a wavelet–chaos–neural network methodology for EEG-based diagnosis of autistic spectrum disorder, *J. Clin. Neurophysiol.* 27 (2010) 328–333.
  - [237] S. Khan, A. Gramfort, N.R. Shetty, M.G. Kitzbichler, S. Ganesan, J.M. Moran, S.M. Lee, J.D. Gabrieli, H.B. Tager-Flusberg, R.M. Joseph, M.R. Herbert, M.S. Hamalainen, T. Kenet, Local and long-range functional connectivity is reduced in concert in autism spectrum disorders, *PNAS* (2013).
  - [238] H. Hinrikus, M. Bachmann, J. Lass, R. Tomson, V. Tuulik, Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms, *Int. J. Radiat. Biol.* 84 (2008) 69–79.
  - [239] A.A. Marino, S. Carrubba, The effects of mobile-phone electromagnetic fields on brain electrical activity: a critical analysis of the literature, *Electromagn. Biol. Med.* 28 (2009) 250–274.
  - [240] F. Vecchio, C. Babiloni, F. Ferreri, G. Curcio, R. Fini, C. Del Percio, P.M. Rossini, Mobile phone emission modulates interhemispheric functional coupling of EEG alpha rhythms, *Eur. J. Neurosci.* 25 (2007) 1908–1913.
  - [241] J.E. Tattersall, I.R. Scott, S.J. Wood, J.J. Nettell, M.K. Bevir, Z. Wang, N.P. Somasiri, X. Chen, Effects of low intensity radiofrequency electromagnetic fields on electrical activity in rat hippocampal slices, *Brain Res.* 904 (2001) 43–53.
  - [242] C.D. Hountala, A.E. Maganioti, C.C. Papageorgiou, E.D. Nanou, M.A. Kyprianou, V.G. Tsiafakis, A.D. Rabavilas, C.N. Capsalis, The spectral power coherence of the EEG under different EMF conditions, *Neurosci. Lett.* 441 (2008) 188–192.
  - [243] M. Bachmann, J. Lass, J. Kalda, M. Sakki, R. Tomson, V. Tuulik, H. Hinrikus, Integration of differences in EEG analysis reveals changes in human EEG caused by microwave, *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 1 (2006) 1597–1600.

- [244] J. Robledo, A.M. Donnellan, K. Strandt-Conroy, An exploration of sensory and movement differences from the perspective of individuals with autism, *Front. Integr. Neurosci.* 6 (2012) 107.
- [245] W. Perry, A. Minassian, B. Lopez, L. Maron, A. Lincoln, Sensorimotor gating deficits in adults with autism, *Biol. Psychiatry*. 61 (2007) 482–486.
- [246] R. Sacco, P. Curatolo, B. Manzi, R. Militeri, C. Bravaccio, A. Frolli, C. Lenti, M. Saccani, M. Elia, K.L. Reichelt, T. Pascucci, S. Puglisi-Allegra, A.M. Persico, Principal pathogenetic components and biological endophenotypes in autism spectrum disorders, *Autism Res.* 3 (2010) 237–252.
- [247] T. Kenet, Sensory functions in ASD, in: D. Fein (Ed.), *The Neuropsychology of Autism*, Oxford University Press, New York, 2011, pp. 215–224.
- [248] E.J. Marco, L.B. Hinkley, S.S. Hill, S.S. Nagarajan, Sensory processing in autism: a review of neurophysiologic findings, *Pediatr. Res.* 69 (2011) 48R–54R.
- [249] T. Kenet, R.C. Froemke, C.E. Schreiner, I.N. Pessah, M.M. Merzenich, Perinatal exposure to a noncoplanar polychlorinated biphenyl alters tonotopy, receptive fields, and plasticity in rat primary auditory cortex, *PNAS* 104 (2007) 7646–7651.
- [250] I.N. Pessah, P.J. Lein, Evidence for environmental susceptibility in autism: what we need to know about gene  $\times$  environment interactions, *Humana* (2008).
- [251] M. Stamou, K.M. Streifel, P.E. Goines, P.J. Lein, Neuronal connectivity as a convergent target of gene–environment interactions that confer risk for autism spectrum disorders, *Neurotoxicol. Teratol.* (2012).
- [252] R. Andrzejak, R. Poreba, M. Poreba, A. Derkacz, R. Skalik, P. Gac, B. Beck, A. Steinmetz-Beck, W. Pilecki, The influence of the call with a mobile phone on heart rate variability parameters in healthy volunteers, *Ind. Health* 46 (2008) 409–417.
- [253] S. Szmigielski, A. Bortkiewicz, E. Gadzicka, M. Zmyslony, R. Kubacki, Alteration of diurnal rhythms of blood pressure and heart rate to workers exposed to radiofrequency electromagnetic fields, *Blood Press. Monit.* 3 (1998) 323–330.
- [254] A. Bortkiewicz, E. Gadzicka, M. Zmyslony, W. Szymczak, Neurovegetative disturbances in workers exposed to 50 Hz electromagnetic fields, *Int. J. Occup. Med. Environ. Health* 19 (2006) 53–60.
- [255] C. Graham, M.R. Cook, A. Sastre, M.M. Gerkovich, R. Kavet, Cardiac autonomic control mechanisms in power-frequency magnetic fields: a multistudy analysis, *Environ. Health. Perspect.* 108 (2000) 737–742.
- [256] R.D. Saunders, J.G. Jefferys, A neurobiological basis for ELF guidelines, *Health Phys.* 92 (2007) 596–603.
- [257] K. Buchner, H. Eger, Changes of clinically important neurotransmitters under the influence of modulated RF fields—a long-term study under real-life conditions (translated; original study in German), *Umwelt-Medizin-Gesellschaft* 24 (2011) 44–57.
- [258] C.V. Bellieni, M. Acampa, M. Maffei, S. Maffei, S. Perrone, I. Pinto, N. Stacchini, G. Buonocore, Electromagnetic fields produced by incubators influence heart rate variability in newborns, *Arch. Dis. Child Fetal. Neonatal.* Ed. 93 (2008) F298–F301.
- [259] F.R. Witter, A.W. Zimmerman, J.P. Reichmann, S.L. Connors, In utero beta 2 adrenergic agonist exposure and adverse neurophysiologic and behavioral outcomes, *Am. J. Obstet. Gynecol.* 201 (2009) 553–559.
- [260] C.J. Anderson, J. Colombo, Larger tonic pupil size in young children with autism spectrum disorder, *Dev. Psychobiol.* 51 (2009) 207–211.
- [261] C.J. Anderson, J. Colombo, K.E. Unruh, Pupil and salivary indicators of autonomic dysfunction in autism spectrum disorder, *Dev. Psychobiol.* (2012).
- [262] C. Daluwatte, J.H. Miles, S.E. Christ, D.Q. Beversdorf, T.N. Takahashi, G. Yao, Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder, *J. Autism Dev. Disord.* (2012).
- [263] X. Ming, J.M. Bain, D. Smith, M. Brimacombe, G. Gold von-Simson, F.B. Axelrod, Assessing autonomic dysfunction symptoms in children: a pilot study, *J. Child Neurol.* 26 (2011) 420–427.
- [264] W. Hirstein, P. Iversen, V.S. Ramachandran, Autonomic responses of autistic children to people and objects, *Proc. Biol. Sci.* 268 (2001) 1883–1888.
- [265] M. Toichi, Y. Kamio, Paradoxical autonomic response to mental tasks in autism, *J. Autism Dev. Disord.* 33 (2003) 417–426.
- [266] X. Ming, P.O. Julu, M. Brimacombe, S. Connor, M.L. Daniels, Reduced cardiac parasympathetic activity in children with autism, *Brain Dev.* 27 (2005) 509–516.
- [267] K.J. Mathewson, I.E. Drmic, M.K. Jetha, S.E. Bryson, J.O. Goldberg, G.B. Hall, D.L. Santesso, S.J. Segalowitz, L.A. Schmidt, Behavioral and cardiac responses to emotional stroop in adults with autism spectrum disorders: influence of medication, *Autism Res.* 4 (2011) 98–108.
- [268] W.P. Cheshire, Highlights in clinical autonomic neuroscience: new insights into autonomic dysfunction in autism, *Auton. Neurosci.* 171 (2012) 4–7.
- [269] M.C. Chang, L.D. Parham, E.I. Blanche, A. Schell, C.P. Chou, M. Dawson, F. Clark, Autonomic and behavioral responses of children with autism to auditory stimuli, *Am. J. Occup. Ther.* 66 (2012) 567–576.
- [270] A. Narayanan, C.A. White, S. Saklayen, M.J. Scaduto, A.L. Carpenter, A. Abduljalil, P. Schmalbrock, D.Q. Beversdorf, Effect of propranolol on functional connectivity in autism spectrum disorder—a pilot study, *Brain Imaging Behav.* 4 (2010) 189–197.
- [271] M.E. Hasselmo, C. Linster, M. Patil, D. Ma, M. Cekic, Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio, *J. Neurophysiol.* 77 (1997) 3326–3339.
- [272] W. Adey, A growing scientific consensus on the cell and molecular biology mediating interactions with EM fields, *Symposium on Electromagnetic Transmissions, Health Hazards, Scientific Evidence and Recent Steps in Mitigation*, 1994.
- [273] G. Buzsaki, *Rhythms of the Brain*, Oxford University Press, New York, 2006.
- [274] S. Strogatz, *Sync: The Emerging Science of Spontaneous Order*, Hyperion, New York, 2003.
- [275] S.H. Strogatz, Exploring complex networks, *Nature* 410 (2001) 268–276.
- [276] S. Iotti, M. Borsari, D. Bendahan, Oscillations in energy metabolism, *Biochim. Biophys. Acta* 1797 (2010) 1353–1361.
- [277] S.H. Strogatz, R.E. Kronauer, C.A. Czeisler, Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia, *Am. J. Physiol.* 253 (1987) R172–R178.
- [278] J.P. Welsh, E.S. Ahn, D.G. Placantonakis, Is autism due to brain desynchronization? *Int. J. Dev. Neurosci.* 23 (2005) 253–263.
- [279] G.M. Anderson, Conceptualizing autism: the role for emergence, *J. Am. Acad. Child Adolesc. Psychiatry*. 48 (2009) 688–691.
- [280] G.M. Anderson, The potential role for emergence in autism, *Autism Res.* 1 (2008) 18–30.
- [281] R.A. Sieb, The emergence of consciousness, *Med. Hypotheses* 63 (2004) 900–904.
- [282] L.B. Smith, E. Thelen, Development as a dynamic system, *Trends Cogn. Sci.* 7 (2003) 343–348.
- [283] R.J. Custodio, C.E. Junior, S.L. Milani, A.L. Simoes, M. de Castro, A.C. Moreira, The emergence of the cortisol circadian rhythm in monozygotic and dizygotic twin infants: the twin-pair synchrony, *Clin. Endocrinol. (Oxf)* 66 (2007) 192–197.
- [284] M. Herbert, Emergent Systems Features, *AutismWHYandHOW.org*, 2012.
- [285] J.M. Krueger, D.M. Rector, S. Roy, H.P. Van Dongen, G. Belenky, J. Panksepp, Sleep as a fundamental property of neuronal assemblies, *Nat. Rev. Neurosci.* 9 (2008) 910–919.
- [286] J.M. Krueger, F. Obal Jr., Sleep function, *Front. Biosci.* 8 (2003) d511–d519.
- [287] J. Juutilainen, T. Kumlin, Occupational magnetic field exposure and melatonin: interaction with light-at-night, *Bioelectromagnetics* 27 (2006) 423–426.



- [288] J. Juutilainen, T. Kumlin, J. Naarala, Do extremely low frequency magnetic fields enhance the effects of environmental carcinogens? A meta-analysis of experimental studies, *Int. J. Radiat. Biol.* 82 (2006) 1–12.
- [289] L. Verschaeve, P. Heikkinen, G. Verheyen, U. Van Gorp, F. Boonen, F. Vander Plaetse, A. Maes, T. Kumlin, J. Maki-Paakkanen, L. Puranen, J. Juutilainen, Investigation of co-genotoxic effects of radiofrequency electromagnetic fields in vivo, *Radiat. Res.* 165 (2006) 598–607.
- [290] A. Ahlbom, J. Bridges, R. de Seze, L. Hillert, J. Juutilainen, M.O. Mattsson, G. Neubauer, J. Schuz, M. Simko, K. Broman, Possible effects of electromagnetic fields (EMF) on human health—opinion of the scientific committee on emerging and newly identified health risks (SCENIHR), *Toxicology* 246 (2008) 248–250.
- [291] A. Hoyto, J. Luukkonen, J. Juutilainen, J. Naarala, Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants, *Radiat. Res.* 170 (2008) 235–243.
- [292] J. Juutilainen, Do electromagnetic fields enhance the effects of environmental carcinogens? *Radiat. Prot. Dosimetry* 132 (2008) 228–231.
- [293] J. Luukkonen, P. Hakulinen, J. Maki-Paakkanen, J. Juutilainen, J. Naarala, Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872 MHz radiofrequency radiation, *Mutat. Res.* 662 (2009) 54–58.
- [294] A. Markkanen, J. Juutilainen, J. Naarala, Pre-exposure to 50 Hz magnetic fields modifies menadione-induced DNA damage response in murine L929 cells, *Int. J. Radiat. Biol.* 84 (2008) 742–751.
- [295] M. King, P. Bearman, Diagnostic change and the increased prevalence of autism, *Int. J. Epidemiol.* 38 (2009) 1224–1234.
- [296] I. Hertz-Picciotto, L. Delwiche, The rise in autism and the role of age at diagnosis, *Epidemiology* 20 (2009) 84–90.
- [297] M.R. Herbert, K. Weintraub, *The Autism Revolution: Whole Body Strategies for Making Life All It Can Be*, Random House with Harvard Health Publications, New York, NY, 2012.
- [298] M. Blank, Electromagnetic fields, in: O. Hanninen (Ed.), *Pathophysiology* 19 (2–3) (2009).
- [299] C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012 <http://www.bioinitiative.org>
- [300] A. Fragopoulou, Y. Grigoriev, O. Johansson, L.H. Margaritis, L. Morgan, E. Richter, C. Sage, Scientific panel on electromagnetic field health risks: consensus points, recommendations, and rationales, *Rev. Environ. Health.* 25 (2010) 307–317.
- [301] C. Sage, D.O. Carpenter, Public health implications of wireless technologies, *Pathophysiology* 16 (2009) 233–246.
- [302] R. Roche, CTIA Wireless Industry Indices Report, Now available at: <http://blog.ctia.org/2012/05/17/indices-report/#comment-41703>
- [303] Cellular Telephone Industry of America (CTIA), *Wireless Quick Facts: Midyear Figures, 2012*, Available at: <http://www.ctia.org/advocacy/research/index.cfm/aid/10323>
- [304] M. Reardon, *Emerging Markets Fuel Cell Phone Growth, 2007*, Available at: <http://news.cnet.com/Emerging-markets-fuel-cell-phone-growth/2100-1039-3615949.html>
- [305] Anonymous, 2.14 Billion Cell Phone Subscribers in 2005, *Softpedia*, 2005, May 20.
- [306] C. Sage, O. Johansson, S.A. Sage, Response to comment on “Personal digital assistant (PDA) cell phone units produce elevated extremely-low frequency electromagnetic field emissions”, *Bioelectromagnetics* 28 (2007) 581–582.
- [307] International Agency for Research on Cancer of the World Health Organization, IARC Classifies Radiofrequency Electromagnetic Fields as Possibly Carcinogenic to Humans, International Agency for Research on Cancer of the World Health Organization, Lyons, France, 2011, May <http://www.iarc.fr/en/media-centre/pr/2011/pdfs/pr2208.E.pdf>
- [308] R. Baan, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, F. Islami, L. Galichet, K. Straif, Carcinogenicity of radiofrequency electromagnetic fields, *Lancet Oncol.* 12 (2011) 624–626.
- [309] C. Sage, O. Johansson, S.A. Sage, Personal digital assistant (PDA) cell phone units produce elevated extremely-low frequency electromagnetic field emissions, *Bioelectromagnetics* 28 (2007) 386–392.
- [310] R. Barouki, P.D. Gluckman, P. Grandjean, M. Hanson, J.J. Heindel, Developmental origins of non-communicable disease: implications for research and public health, *Environ. Health* 11 (42) (2012) 1–9.
- [311] N.C. Derecki, J.C. Cronk, Z. Lu, E. Xu, S.B. Abbott, P.G. Guyenet, J. Kipnis, Wild-type microglia arrest pathology in a mouse model of Rett syndrome, *Nature* 484 (2012) 105–109.
- [312] N.C. Derecki, J.C. Cronk, J. Kipnis, The role of microglia in brain maintenance: implications for Rett syndrome, *Trends Immunol.* (2012).
- [313] P. Krakowiak, C.K. Walker, A.A. Bremer, A.S. Baker, S. Ozonoff, R.L. Hansen, I. Hertz-Picciotto, Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders, *Pediatrics* 129 (2012) e1121–e1128.
- [314] D. Noble, *The Music of Life: Biology Beyond the Genome*, Oxford University Press, New York, 2006.
- [315] M. Herbert, Autism: from static genetic brain defect to dynamic gene-environment modulated pathophysiology, in: S. Krimsky, J. Gruber (Eds.), *Genetic Explanations: Sense and Nonsense*, Harvard University Press, Cambridge, MA, 2013, pp. 122–146.
- [316] L. Cristofolini, F. Taddei, M. Baleani, F. Baruffaldi, S. Stea, M. Viceconti, Multiscale investigation of the functional properties of the human femur, *Philos. Trans. A: Math. Phys. Eng. Sci.* 366 (2008) 3319–3341.
- [317] A.A. de Graaf, A.P. Freidig, B. De Roos, N. Jamshidi, M. Heinemann, J.A. Rullmann, K.D. Hall, M. Adiels, B. van Ommen, Nutritional systems biology modeling: from molecular mechanisms to physiology, *PLoS Comput. Biol.* 5 (2009) e1000554.
- [318] D. Majumder, A. Mukherjee, A passage through systems biology to systems medicine: adoption of middle-out rational approaches towards the understanding of therapeutic outcomes in cancer, *Analyst* 136 (2011) 663–678.
- [319] S. Vinga, A.R. Neves, H. Santos, B.W. Brandt, S.A. Koijman, Subcellular metabolic organization in the context of dynamic energy budget and biochemical systems theories, *Philos. Trans. R. Soc. London, Ser. B* 365 (2010) 3429–3442.
- [320] D.C. Walker, J. Southgate, The virtual cell—a candidate co-ordinator for ‘middle-out’ modelling of biological systems, *Brief. Bioinform.* 10 (2009) 450–461.
- [321] K. Mann, J. Roschke, Effects of pulsed high-frequency electromagnetic fields on human sleep, *Neuropsychobiology* 33 (1996) 41–47.
- [322] A. Fragopoulou, L. Margaritis, Evidence for EMF Transcriptomics and Proteomics Research (2007–2012), in: C. Sage, D.O. Carpenter (Eds.), *The BioInitiative Report 2012: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, 2012 (Section 5) <http://www.bioinitiative.org>
- [323] E. Mumper, Can awareness of medical pathophysiology in autism lead to primary care autism prevention strategies, *N. Am. J. Med. Sci.* 6 (3) (2013) 134–144.

Fertility; Research Abstracts, List of References Reporting Fertility and/  
or Reproduction Effects from Electromagnetic Fields and/or  
Radiofrequency Radiation (66 references)

## **List of References Reporting Fertility and/or Reproduction Effects from Electromagnetic Fields and/or Radiofrequency Radiation (66 references)**

**(with abstracts)**

**Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. (2008) Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. *Fertility and Sterility* 89(1):124-8.**

OBJECTIVE: To investigate the effect of cell phone use on various markers of semen quality.

DESIGN: Observational study.

SETTING: Infertility clinic.

PATIENT(S): Three hundred sixty-one men undergoing infertility evaluation were divided into four groups according to their active cell phone use: group A: no use; group B: <2 h/day; group C: 2-4 h/day; and group D: >4 h/day.

INTERVENTION(S): None.

MAIN OUTCOME MEASURE(S): Sperm parameters (volume, liquefaction time, pH, viscosity, sperm count, motility, viability, and morphology).

RESULT(S): The comparisons of mean sperm count, motility, viability, and normal morphology among four different cell phone user groups were statistically significant. Mean sperm motility, viability, and normal morphology were significantly different in cell phone user groups within two sperm count groups. The laboratory values of the above four sperm parameters decreased in all four cell phone user groups as the duration of daily exposure to cell phones increased.

CONCLUSION(S): Use of cell phones decrease the semen quality in men by decreasing the sperm count, motility, viability, and normal morphology. The decrease in sperm parameters was dependent on the duration of daily exposure to cell phones and independent of the initial semen quality.

**(Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, Sharma R)  
Agarwal A, Desai NR, Makker K, et al. (2009) Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. *Fertility and Sterility* 92(4):1318-25.**

OBJECTIVE: To evaluate effects of cellular phone radiofrequency electromagnetic waves (RF-EMW) during talk mode on unprocessed (neat) ejaculated human semen.

DESIGN: Prospective pilot study.

SETTING: Center for reproductive medicine laboratory in tertiary hospital setting.

SAMPLES: Neat semen samples from normal healthy donors (n = 23) and infertile patients (n = 9).

INTERVENTION(S): After liquefaction, neat semen samples were divided into two aliquots. One aliquot (experimental) from each patient was exposed to cellular phone radiation (in talk mode) for 1 h, and the second aliquot (unexposed) served as the control sample under identical conditions.

MAIN OUTCOME MEASURE(S): Evaluation of sperm parameters (motility, viability), reactive oxygen species (ROS), total antioxidant capacity (TAC) of semen, ROS-TAC score, and sperm DNA damage.

RESULT(S): Samples exposed to RF-EMW showed a significant decrease in sperm motility and viability, increase in ROS level, and decrease in ROS-TAC score. Levels of TAC and DNA damage showed no significant differences from the unexposed group.

**CONCLUSION(S): Radiofrequency electromagnetic waves emitted from cell phones may lead to oxidative stress in human semen. We speculate that keeping the cell phone in a trouser pocket in talk mode may negatively affect spermatozoa and impair male fertility.**

**Agarwal A, Desai NR, Ruffoli R, Carpi A. (2008) Lifestyle and testicular dysfunction: a brief update. Biomed Pharmacother. 62(8):550-3.**

The incidence of testicular cancer, cryptorchidism and defective spermatogenesis is increasing probably due to environmental and lifestyle-related factors. The aim of this review is to briefly describe and comment on the principal lifestyle factors. The recent findings that the electromagnetic waves following the use of the cell phone and the prolonged exposure to the noise stress cause relevant testicular dysfunction in man or animals reinforce the hypothesis of the importance of lifestyle-related factors.

**Agarwal A, Singh A, Hamada A, Kesari K (2011) Cell phones and male infertility: a review of recent innovations in technology and consequences. Brazilian Journal of Urology 37(4):432-54.**

Cell phones have become a vital part of everyday life. However, the health risks associated with their usage are often overlooked. Recently, evidence from several studies supports a growing claim that cell phone usage may have a detrimental effect on sperm parameters leading to decreased male fertility. Nonetheless, other studies showed no conclusive link between male infertility and cell phone usage. The ambiguity of such results is attributed to the lack of a centralized assay for measuring inflicted damage caused by cell phones. Study design, ethics, and reproducibility are all aspects which must be standardized before any conclusions can be made.

**Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM, King BV (2005) Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline. International Journal of Andrology 28(3):179-179.**

Concern has arisen over human exposures to radio frequency electromagnetic radiation (RFEMR), including a recent report indicating that regular mobile phone use can negatively impact upon human semen quality. These effects would be particularly serious if the biological effects of RFEMR included the induction of DNA damage in male germ cells. In this study, mice were exposed to 900 MHz RFEMR at a specific absorption rate of approximately 90 mW/kg inside a waveguide for 7 days at 12 h per day. Following exposure, DNA damage to caudal epididymal spermatozoa was assessed by quantitative PCR (QPCR) as well as alkaline and pulsed-field gel electrophoresis. The treated mice were overtly normal and all assessment criteria, including sperm number, morphology and vitality were not significantly affected. Gel electrophoresis revealed no gross evidence of increased single- or double-DNA strand breakage in spermatozoa taken from treated animals. However, a detailed analysis of DNA integrity using QPCR revealed statistically significant damage to both the mitochondrial genome ( $p < 0.05$ ) and the nuclear beta-globin locus ( $p < 0.01$ ). This study suggests that while RFEMR does not have a dramatic impact on male germ cell development, a significant genotoxic effect on epididymal spermatozoa is evident and deserves further investigation.

**Avendaño C, Mata A, Sanchez Sarmiento CA, Doncel GF (2012) Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertility and Sterility [Epub ahead of print]**

**OBJECTIVE:** To evaluate the effects of laptop computers connected to local area networks wirelessly (Wi-Fi) on human spermatozoa.

**DESIGN:** Prospective in vitro study.

**SETTING:** Center for reproductive medicine.

**PATIENT(S):** Semen samples from 29 healthy donors.

**INTERVENTION(S):** Motile sperm were selected by swim up. Each sperm suspension was divided into two aliquots. One sperm aliquot (experimental) from each patient was exposed to an internet-connected laptop by Wi-Fi for 4 hours, whereas the second aliquot (unexposed) was used as control, incubated under identical conditions without being exposed to the laptop.



**MAIN OUTCOME MEASURE(S):** Evaluation of sperm motility, viability, and DNA fragmentation.

**RESULT(S):** Donor sperm samples, mostly normozoospermic, exposed ex vivo during 4 hours to a wireless internet-connected laptop showed a significant decrease in progressive sperm motility and an increase in sperm DNA fragmentation. Levels of dead sperm showed no significant differences between the two groups.

**CONCLUSION(S):** To our knowledge, this is the first study to evaluate the direct impact of laptop use on human spermatozoa. Ex vivo exposure of human spermatozoa to a wireless internet-connected laptop decreased motility and induced DNA fragmentation by a nonthermal effect. We speculate that keeping a laptop connected wirelessly to the internet on the lap near the testes may result in decreased male fertility. Further in vitro and in vivo studies are needed to prove this contention.

**Awad H, Halawa F, Mostafa T, Atta H. (2006) Melatonin hormone profile in infertile males. International Journal of Andrology 29(3):409-13.**

Melatonin is a hormone produced by the pineal gland. There is much controversy about its relationship to the male reproductive process. In this study, seminal plasma as well as the serum melatonin levels were studied in different infertile male groups and were correlated with their semen parameters and hormonal levels. One hundred twenty male cases subdivided into six equal groups were consecutively included; fertile normozoospermic men, oligoasthenozoospermia (OA), OA with leucocytospermia, OA with varicocele, non-obstructive azoospermia (NOA) with high serum follicle stimulating hormone (FSH) and NOA with normal FSH. Semen analysis, estimation of melatonin, FSH, testosterone (T) and prolactin (PRL) hormone was carried out. Mean level of serum melatonin was higher than its corresponding seminal concentrations in all investigated groups with a positive correlation between their levels ( $r = 0.532$ ,  $p = 0.01$ ). Serum and seminal plasma melatonin levels in all infertile groups were reduced significantly compared with their levels in the fertile group. The lowest concentrations were in OA with leucocytospermia group. Melatonin in both serum and semen demonstrated significant correlation with sperm motility ( $r = 0.607$ ,  $0.623$  respectively,  $p = 0.01$ ). Serum melatonin correlated positively with serum PRL ( $r = 0.611$ ,  $p = 0.01$ ). It may be concluded that melatonin may be involved in the modulation of reproductive neuroendocrine axis in male infertility. Also, low levels of melatonin in semen were observed in infertile groups having reduced sperm motility, leucocytospermia, varicocele and NOA.

**Balmori A (2009) Electromagnetic pollution from phone masts. Effects on wildlife. Pathophysiology 16(2-3):191-9.**

A review on the impact of radiofrequency radiation from wireless telecommunications on wildlife is presented. Electromagnetic radiation is a form of environmental pollution which may hurt wildlife. Phone masts located in their living areas are irradiating continuously some species that could suffer long-term effects, like reduction of their natural defenses, deterioration of their health, problems in reproduction and reduction of their useful territory through habitat deterioration. Electromagnetic radiation can exert an aversive behavioral response in rats, bats and birds such as sparrows. Therefore microwave and radiofrequency pollution constitutes a potential cause for the decline of animal populations and deterioration of health of plants living near phone masts. To measure these effects urgent specific studies are necessary.

**Baste V, Riise T, Moen BE (2008) Radiofrequency electromagnetic fields; male infertility and sex ratio of offspring. European Journal of Epidemiology 23(5):369-77.**

Concern is growing about exposure to electromagnetic fields and male reproductive health. The authors performed a cross-sectional study among military men employed in the Royal Norwegian Navy, including information about work close to equipment emitting radiofrequency electromagnetic fields, one-year infertility, children and sex of the offspring. Among 10,497 respondents, 22% had worked close to high-frequency aerials to a "high" or "very high" degree. Infertility increased significantly along with increasing self-reported exposure to radiofrequency electromagnetic fields. In a logistic regression, odds ratio (OR) for infertility among those who had

worked closer than 10 m from high-frequency aeriels to a "very high" degree relative to those who reported no work near high-frequency aeriels was 1.86 (95% confidence interval (CI): 1.46-2.37), adjusted for age, smoking habits, alcohol consumption and exposure to organic solvents, welding and lead. Similar adjusted OR for those exposed to a "high", "some" and "low" degree were 1.93 (95% CI: 1.55-2.40), 1.52 (95% CI: 1.25-1.84), and 1.39 (95% CI: 1.15-1.68), respectively. In all age groups there were significant linear trends with higher prevalence of involuntary childlessness with higher self-reported exposure to radiofrequency fields. However, the degree of exposure to radiofrequency radiation and the number of children were not associated. For self-reported exposure both to high-frequency aeriels and communication equipment there were significant linear trends with lower ratio of boys to girls at birth when the father reported a higher degree of radiofrequency electromagnetic exposure.

**Behari J, Kesari KK (2006) Effects of microwave radiations on reproductive system of male rats. Embryo Talk 1 (Suppl.1):81-5.**

Recently, there have been reports referring to studies on health effects due to exposure of radiofrequency electromagnetic radiation (RFEMR). In this context mobile phones are often being implicated. In an attempt to quantitate this study was undertaken to examine their exposure effects. Animals were exposed continuously to 900 MHz Frequency at a specific absorption rate of approximately 0.9 W/Kg for 35 days at 2 hours per day. Rats were placed in Plexiglas cages with drilled ventilation holes, which have been attached with mobile phone hand set. After the exposure period, rats were immediately sacrificed and sperms were collected for the study of DNA double strand breaks by microgel electrophoresis (Comet assay), sperm count and testis weight was taken. To confirm this at other frequencies animals were exposed to low intensity microwaves (2.45 GHz, 0.34 mW/cm<sup>2</sup> SAR 0.1 W/Kg). A similar set of studies was undertaken after the exposure period, when the animals were similarly sacrificed. Results obtained using the mobile phone exposure shows that the chronic exposure to these radiations cause double strand DNA breaks in sperm cells. This study also shows that the mobile radiation exposure can cause statistically significant decrease in the sperm count and testes weight. A similar set of data was obtained from 2.45 GHz exposure. It is concluded that microwave induced effects on reproductive system are uniformly distributed over the electromagnetic spectrum under investigation.

**Belyaev IY, Grigoriev YG (2007) Problems in assessment of risks from exposures to microwaves of mobile communication. Radiatsionnaya biologiya, radioecologiya / Rossiyskaya akademiya nauk 47(6):727-32.**

Since pioneering investigations published in the beginning of 1970th, various biological responses to non-thermal (NT) microwaves (MW), including adverse health effects, have been described by many research groups all over the world. There is strong evidence that the NT MW biological effects depend on several physical parameters and biological variables, which must be controlled in replication studies. Apart from the fundamental importance, the development of comprehensive mechanisms for the NT MW effects is socially important. The effects of MW of mobile communications are of major concern because of the increased exposure in many countries. It has been shown that adverse effects of NT MW from GSM/UMTS mobile phones on human lymphocytes from healthy and hypersensitive to EMF persons depend on carrier frequency and modulation. Further investigations with human primary cells, animals and volunteers are needed to elucidate possible adverse effects of MW signals that are used in wireless communication. Identification of those types and frequency channels/bands for mobile communication, which do not affect human cells, is urgently needed as the high priority task for the development of safe mobile communication. Numerous data on the NT MW effects clearly indicate that the SAR-concept alone cannot underlie the safety guidelines for chronic exposures to MW from mobile communication and other approaches are needed. However, there is not enough research information to set exposure MW standards. Various genetic and epigenetic effects of signals used in mobile communication should be studied. It has been shown that NT MW affect cells of various types including stem cells and reproductive organs. Stem cells represent especially important cellular model because recent data suggest that different cancer types, including leukemia, have a fundamentally common basis that is grounded on epigenetic changes in stem cells.

**Blank M, Goodman R (2011) DNA is a fractal antenna in electromagnetic fields. International Journal of Radiation Biology 87(4):409-15.**

**PURPOSE:** To review the responses of deoxyribonucleic acid (DNA) to electromagnetic fields (EMF) in different frequency ranges, and characterise the properties of DNA as an antenna.

**MATERIALS AND METHODS:** We examined published reports of increased stress protein levels and DNA strand breaks due to EMF interactions, both of which are indicative of DNA damage. We also considered antenna properties such as electronic conduction within DNA and its compact structure in the nucleus.

**RESULTS:** EMF interactions with DNA are similar over a range of non-ionising frequencies, i.e., extremely low frequency (ELF) and radio frequency (RF) ranges. There are similar effects in the ionising range, but the reactions are more complex.

**CONCLUSIONS:** The wide frequency range of interaction with EMF is the functional characteristic of a fractal antenna, and DNA appears to possess the two structural characteristics of fractal antennas, electronic conduction and self symmetry. These properties contribute to greater reactivity of DNA with EMF in the environment, and the DNA damage could account for increases in cancer epidemiology, as well as variations in the rate of chemical evolution in early geologic history.

**Davoudi M, Brossner C, Kuber W (2002) Der Einfluelektromagnetischer Wellen auf die Spermienmotilit. Journal Für Urologie Und Urogynäkologie 9(3):18-22.**

**Objective:** To evaluate the influence of electromagnetic waves (EMW) caused by mobile phones on sperm motility.

**Methods:** 13 men with a normal spermiogramm regarding the WHO criteria were included in our study. After a GSM-mobile phone was not carried or used during 5 days a first spermiogramm was analysed. Four weeks later, a second spermiogramm was performed. Five days before this second spermiogramm, men carried the mobile phone on the belt and used it 6 hours a day intensively. Spermiogramm parameters of the first and second spermiogramm were compared.

**Results:** Rapid progressive spermatozoa were reduced significantly in the second spermiogramm compared to the first. Decrease was from (mean) 32.3 % (SD  $\pm$  6.13) to (mean) 26.1 % (SD  $\pm$  6.5),  $p = 0.0004$ . In addition there was a shift to an increase of progressive spermatozoa from mean 24.8 % (SD  $\pm$  3.62) to 29.7 % (SD  $\pm$  6.11),  $p = 0.01$ . All other spermiogramm parameters like semen volume, density and morphology did not differ significantly.

**Conclusion:** Our data suggest a decreased motility of rapid progressive spermatozoa caused by electromagnetic waves of GSM-mobile phones. These findings may have an impact in counselling subfertile men.

**Deepinder F, Makker K, Agarwal A (2007) Cell phones and male infertility: dissecting the relationship. Reproductive Biomedicine Online 15(3):266-70.**

There has been a tremendous increase in the use of mobile phones in the past decade and concerns are growing about the possible hazardous effects of radio-frequency electromagnetic waves (EMW) emitted by these devices on human health. Preliminary studies, though with limitations in study design, suggest a possible link between cell phone use and infertility. A recent study found that use of cell phones adversely affects the quality of semen by decreasing the sperm counts, motility, viability and morphology. Evidence of detrimental effect of mobile phones on male fertility is still equivocal as studies have revealed a wide spectrum of possible effects ranging from insignificant effects to variable degrees of testicular damage. Although previous studies suggested a role of cell phone use in male infertility, the mode of action of EMW emitted from cell phones on the male reproductive system is still unclear. EMW can affect the reproductive system via an EMW-specific effect, thermal molecular effect or combination of both. Studies performed on human males are scarce and therefore further studies with a careful design are needed to determine the effect of cell phone use on male-fertilizing potential.

**De Iuliis GN, Newey RJ, King BV, Aitken RJ (2009) Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. PLoS One 4(7):e6446.**

**BACKGROUND:** In recent times there has been some controversy over the impact of electromagnetic radiation on human health. The significance of mobile phone radiation on male reproduction is a key element of this debate since several studies have suggested a relationship between mobile phone use and semen quality. The potential mechanisms involved have not been established, however, human spermatozoa are known to be particularly vulnerable to oxidative stress by virtue of the abundant availability of substrates for free radical attack and the lack of cytoplasmic space to accommodate antioxidant enzymes. Moreover, the induction of oxidative stress in these cells not only perturbs their capacity for fertilization but also contributes to sperm DNA damage. The latter has, in turn, been linked with poor fertility, an increased incidence of miscarriage and morbidity in the offspring, including childhood cancer. In light of these associations, we have analyzed the influence of RF-EMR on the cell biology of human spermatozoa in vitro.

**PRINCIPAL FINDINGS:** Purified human spermatozoa were exposed to radio-frequency electromagnetic radiation (RF-EMR) tuned to 1.8 GHz and covering a range of specific absorption rates (SAR) from 0.4 W/kg to 27.5 W/kg. In step with increasing SAR, motility and vitality were significantly reduced after RF-EMR exposure, while the mitochondrial generation of reactive oxygen species and DNA fragmentation were significantly elevated ( $P < 0.001$ ). Furthermore, we also observed highly significant relationships between SAR, the oxidative DNA damage bio-marker, 8-OH-dG, and DNA fragmentation after RF-EMR exposure.

**CONCLUSIONS:** RF-EMR in both the power density and frequency range of mobile phones enhances mitochondrial reactive oxygen species generation by human spermatozoa, decreasing the motility and vitality of these cells while stimulating DNA base adduct formation and, ultimately DNA fragmentation. These findings have clear implications for the safety of extensive mobile phone use by males of reproductive age, potentially affecting both their fertility and the health and wellbeing of their offspring.

**Desai NR, Kesari KK, Agarwal A (2009) Pathophysiology of cell phone radiation: oxidative stress and carcinogenesis with focus on male reproductive system. Reproductive Biology and Endocrinology 7:114.**

Hazardous health effects stemming from exposure to radiofrequency electromagnetic waves (RF-EMW) emitted from cell phones have been reported in the literature. However, the cellular target of RF-EMW is still controversial. This review identifies the plasma membrane as a target of RF-EMW. In addition, the effects of RF-EMW on plasma membrane structures (i.e. NADH oxidase, phosphatidylserine, ornithine decarboxylase) and voltage-gated calcium channels are discussed. We explore the disturbance in reactive oxygen species (ROS) metabolism caused by RF-EMW and delineate NADH oxidase mediated ROS formation as playing a central role in oxidative stress (OS) due to cell phone radiation (with a focus on the male reproductive system). This review also addresses: 1) the controversial effects of RF-EMW on mammalian cells and sperm DNA as well as its effect on apoptosis, 2) epidemiological, in vivo animal and in vitro studies on the effect of RF-EMW on male reproductive system, and 3) finally, exposure assessment and dosimetry by computational biomodeling.

**(Erogul O, Oztas E, Yildirim I, Kir T, Aydur E, Komesli G, Irkilata HC, Irmak MK, Peker AF) Erogul O, Oztas E, Yildirim I, et al. (2006) Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study. Archives of Medical Research 37(7):840-3.**

**BACKGROUND:** There has been growing public concern on the effects of electromagnetic radiation (EMR) emitted by cellular phones on human health. Many studies have recently been published on this topic. However, possible consequences of the cellular phone usage on human sperm parameters have not been investigated adequately.

**METHODS:** A total number of 27 males were enrolled in the study. The semen sample obtained from each participant was divided equally into two parts. One of the specimens was exposed to EMR emitted by an activated 900 MHz cellular phone, whereas the other was not. The concentration and motility of the specimens were compared to analyze the effects of EMR. Assessment of sperm movement in all specimens was performed using four criteria: (A) rapid progressive, (B) slow progressive, (C) nonprogressive, (D) no motility.

**RESULTS:** Statistically significant changes were observed in the rapid progressive, slow progressive and no-motility categories of sperm movement. EMR exposure caused a subtle decrease in the rapid progressive and slow progressive sperm movement. It also caused an increase in the no-motility category of sperm movement. There was no statistically significant difference in the sperm concentration between two groups.

**CONCLUSIONS:** These data suggest that EMR emitted by cellular phone influences human sperm motility. In addition to these acute adverse effects of EMR on sperm motility, long-term EMR exposure may lead to behavioral or structural changes of the male germ cell. These effects may be observed later in life, and they are to be investigated more seriously.

**Falzone N, Huyser C, Franken DR, Leszczynski D (2010) Mobile phone radiation does not induce pro-apoptosis effects in human spermatozoa. *Radiation Research* 174(2):169-76.**

Recent reports suggest that mobile phone radiation may diminish male fertility. However, the effects of this radiation on human spermatozoa are largely unknown. The present study examined effects of the radiation on induction of apoptosis-related properties in human spermatozoa. Ejaculated, density-purified, highly motile human spermatozoa were exposed to mobile phone radiation at specific absorption rates (SARs) of 2.0 and 5.7 W/kg. At various times after exposure, flow cytometry was used to examine caspase 3 activity, externalization of phosphatidylserine (PS), induction of DNA strand breaks, and generation of reactive oxygen species. Mobile phone radiation had no statistically significant effect on any of the parameters studied. This suggests that the impairment of fertility reported in some studies was not caused by the induction of apoptosis in spermatozoa.

**Falzone N, Huyser C, Becker P, Leszczynski D, Franken DR (2010) The effect of pulsed 900-MHz GSM mobile phone radiation on the acrosome reaction, head morphometry and zona binding of human spermatozoa. *International Journal of Andrology* 33:1-7.**

**Falzone N, Huyser C, Becker P, Leszczynski D, Franken DR (2011) The effect of pulsed 900-MHz GSM mobile phone radiation on the acrosome reaction, head morphometry and zona binding of human spermatozoa. *International Journal of Andrology* 34(1):20-6.**

Several recent studies have indicated that radiofrequency electromagnetic fields (RF-EMF) have an adverse effect on human sperm quality, which could translate into an effect on fertilization potential. This study evaluated the effect of RF-EMF on sperm-specific characteristics to assess the fertilizing competence of sperm. Highly motile human spermatozoa were exposed for 1 h to 900-MHz mobile phone radiation at a specific absorption rate of 2.0 W/kg and examined at various times after exposure. The acrosome reaction was evaluated using flow cytometry. The radiation did not affect sperm propensity for the acrosome reaction. Morphometric parameters were assessed using computer-assisted sperm analysis. Significant reduction in sperm head area ( $9.2 \pm 0.7 \mu\text{m}^2$  vs.  $18.8 \pm 1.4 \mu\text{m}^2$ ) and acrosome percentage of the head area ( $21.5 \pm 4\%$  vs.  $35.5 \pm 11.4\%$ ) was reported among exposed sperm compared with unexposed controls. Sperm-zona binding was assessed directly after exposure using the hemizona assay. The mean number of zona-bound sperm of the test hemizona and controls was  $22.8 \pm 12.4$  and  $31.8 \pm 12.8$  ( $p < 0.05$ ), respectively. This study concludes that although RF-EMF exposure did not adversely affect the acrosome reaction, it had a significant effect on sperm morphometry. In addition, a significant decrease in sperm binding to the hemizona was observed. These results could indicate a significant effect of RF-EMF on sperm fertilization potential.

**Fejes I, Závaczki Z, Szöllosi J, Koloszar S, Kovacs L, Pál A (2004) Relationship between regular cell phone use and human semen quality. Abstracts of the 20th Annual Meeting of the ESHRE, Berlin, Germany, 27–30 June 2004.**

Introduction: Environmental factors can be responsible for the deteriorative sperm parameters detected in the last decades. The effects of the electromagnetic field of mobile phones ( 900MHz) on human spermatogenesis have not been studied yet. Our aim was to determine possible relationship between regular cell phone use and the different human semen attributes.

Methods: Localisation: University of Szeged, Dept. Obstetrics and Gynaecology, Hungary. History taking was supplemented with questions, how long patient owns mobile phone, how long it is standby in a day (in hours) near the patient, and how long it transmits daily (in minutes). Semen analyses were performed using Makler sperm counting chamber. Sperm concentration, motility according to WHO guidelines, motile sperm count and progressively motile sperm count were assessed. Comparison between non-users and very active users has been drawn. Statistical analyses were performed using SPSS 11.0 software.

Results: A total of 451 patients were examined during the 13 months of study period. Among the 221 men corresponded the criteria and completed the study, significant correlations were found between duration of standby position and sperm concentration ( $r=-0.161$ ,  $p=0.04$ ) length of daily transmission and rapid progressive or slow progressive motility ( $r=-0.191$ ,  $p=0.005$ ;  $r=0.323$ ,  $p<0.001$ , respectively) and between the duration of standby position and rapid progressive motile sperm concentration ( $r=-0.218$ ,  $p=0.005$ ). Furthermore, difference was found between daylong standby and non-standby users in sperm concentration ( $59.11 \times 10^6/\text{ml}$  vs  $82.97 \times 10^6/\text{ml}$ ,  $p=0.021$ ,  $N=51$  vs  $46$ ) and between prolonged transmitters and non-transmitters in rapid progressive motility ( $36.31\%$  vs  $51.34\%$ ,  $p=0.007$ ,  $N=16$  vs  $61$ ). Conclusions: The prolonged use of cell phones may have negative effect on spermatogenesis and male fertility, that presumably deteriorates both concentration and motility. Further controlled randomised studies are necessary to precise the correlation coefficients.

**(Fejes I, Závaczki Z, Szöllosi J, Koloszar S, Daru J, Kovacs L, Pál A)**

**Fejes I, Závaczki Z, Szöllosi J, et al. (2005) Is there a relationship between cell phone use and semen quality? Archives of Andrology 51(5):385-93.**

This study was conducted to determine a possible relationship between regular cell phone use and different human semen attributes. The history-taking of men in our university clinic was supplemented with questions concerning cell phone use habits, including possession, daily standby position and daily transmission times. Semen analyses were performed by conventional methods. Statistics were calculated with SPSS statistical software. A total of 371 were included in the study. The duration of possession and the daily transmission time correlated negatively with the proportion of rapid progressive motile sperm ( $r = -0.12$  and  $r = -0.19$ , respectively), and positively with the proportion of slow progressive motile sperm ( $r = 0.12$  and  $r = 0.28$ , respectively). The low and high transmitter groups also differed in the proportion of rapid progressive motile sperm ( $48.7\%$  vs.  $40.6\%$ ). The prolonged use of cell phones may have negative effects on the sperm motility characteristics.

**(Fragopoulou A, Grigoriev Y, Johansson O, Margaritis LH, Morgan L, Richter E, Sage C)**  
**Fragopoulou A, Grigoriev Y, Johansson O, et al. (2010) Scientific Panel on Electromagnetic Field Health Risks: Consensus points, recommendations, and rationales. Reviews on Environmental Health 25(4):307-17.**

In November, 2009, a scientific panel met in Seletun, Norway, for three days of intensive discussion on existing scientific evidence and public health implications of the unprecedented global exposures to artificial electromagnetic fields (EMF). EMF exposures (static to 300 GHz) result from the use of electric power and from wireless telecommunications technologies for voice and data transmission, energy, security, military and radar use in weather and transportation. The Scientific Panel recognizes that the body of evidence on EMF requires a new approach to protection of public health; the growth and development of the fetus, and of children; and argues for strong

preventative actions. New, biologically-based public exposure standards are urgently needed to protect public health worldwide.

**Girgert R, Gründker C, Emons G, Hanf V (2008) Electromagnetic fields alter the expression of estrogen receptor cofactors in breast cancer cells. *Bioelectromagnetics* 29(3):169-76.**

Breast cancer is the most common malignancy of women in Western societies. The increasing exposure to electromagnetic fields has been suspected to contribute to the rising incidence of breast cancer in industrialized countries. The majority of breast tumors is treated with the partial antiestrogen tamoxifen. Most tumors become resistant to tamoxifen in the course of treatment resulting in treatment failure. Electromagnetic fields reduce the efficacy of tamoxifen similar to tamoxifen resistance. In this study we investigated the mechanism by which electromagnetic fields influence the sensitivity to tamoxifen. In cells exposed to 1.2 microT of a 50 Hz electromagnetic field gene expression of cofactors of the estrogen receptors was compared to sham exposed cells. Using a gene array technology several cofactors were found to be differentially expressed. The expression of the coactivators, SRC-1 and AIB1, and of two corepressors, N-Cor and SMRT, was quantified by RT-PCR. Both coactivators were expressed more strongly in the exposed cells while the expression of two corepressors decreased. The RNA analysis was confirmed by Western blots. The contradirectional changes in gene expression of coactivators and corepressors by electromagnetic fields results in a lower sensitivity to tamoxifen. Electromagnetic fields may contribute to the induction of tamoxifen resistance in vivo.

**(Grigoriev YG, Grigoriev OA, Ivanov AA, Lyaginskaya AM, Merkulov AV, Shagina NB, Maltsev VN, Lévêque P, Ulanova AM, Osipov VA, Shafirkin AV.)  
Grigoriev YG, Grigoriev OA, Ivanov AA, et al. (2010) Confirmation studies of Soviet research on immunological effects of microwaves: Russian immunology results. *Bioelectromagnetics* 31(8):589-602.**

This paper presents the results of a replication study performed to investigate earlier Soviet studies conducted between 1974 and 1991 that showed immunological and reproductive effects of long-term low-level exposure of rats to radiofrequency (RF) electromagnetic fields. The early studies were used, in part, for developing exposure standards for the USSR population and thus it was necessary to confirm the Russian findings. In the present study, the conditions of RF exposure were made as similar as possible to those in the earlier experiments: Wistar rats were exposed in the far field to 2450 MHz continuous wave RF fields with an incident power density in the cages of 5 W/m<sup>2</sup> for 7 h/day, 5 days/week for a total of 30 days, resulting in a whole-body SAR of 0.16 W/kg. Effects of the exposure on immunological parameters in the brain and liver of rats were evaluated using the complement fixation test (CFT), as in the original studies, and an additional test, the more modern ELISA test. Our results, using CFT and ELISA, partly confirmed the findings of the early studies and indicated possible effects from non-thermal RF exposure on autoimmune processes. The RF exposure resulted in minor increases in formation of antibodies in brain tissue extract and the exposure did not appear to be pathological. In addition, a study was conducted to replicate a previous Soviet study on effects from the injection of blood serum from RF-exposed rats on pregnancy and foetal and offspring development of rats, using a similar animal model and protocol. Our results showed the same general trends as the earlier study, suggesting possible adverse effects of the blood serum from exposed rats on pregnancy and foetal development of intact rats, however, application of these results in developing exposure standards is limited.

**Gul A, Celebi H, Uğraş S (2009) The effects of microwave emitted by cellular phones on ovarian follicles in rats. *Archives of Gynecology and Obstetrics* 280(5):729-33.**

**OBJECTIVE:** The aim of this study was to investigate whether there were any toxic effects of microwaves of cellular phones on ovaries in rats.

**METHODS:** In this study, 82 female pups of rats, aged 21 days (43 in the study group and 39 in the control group) were used. Pregnant rats in the study group were exposed to mobile phones that were



placed beneath the polypropylene cages during the whole period of pregnancy. The cage was free from all kinds of materials, which could affect electromagnetic fields. A mobile phone in a standby position for 11 h and 45 min was turned on to speech position for 15 min every 12 h and the battery was charged continuously. On the 21st day after the delivery, the female rat pups were killed and the right ovaries were removed. The volumes of the ovaries were measured and the number of follicles in every tenth section was counted.

**RESULTS:** The analysis revealed that in the study group, the number of follicles was lower than that in the control group. The decreased number of follicles in pups exposed to mobile phone microwaves suggest that intrauterine exposure has toxic effects on ovaries.

**CONCLUSION:** We suggest that the microwaves of mobile phones might decrease the number of follicles in rats by several known and, no doubt, countless unknown mechanisms.

**Gutschi T, Mohamad Al-Ali B, Shamloul R, Pummer K, Trummer H (2011) Impact of cell phone use on men's semen parameters. *Andrologia* 43(5):312-6.**

The objective of the present retrospective study was to report our experience concerning the effects of cell phone usage on semen parameters. We examined 2110 men attending our infertility clinic from 1993 to October 2007. Semen analysis was performed in all patients. Serum free testosterone (T), follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin (PRL) were collected from all patients. The information on cell phone use of the patients was recorded and the subjects were divided into two groups according to their cell phone use: group A: cell phone use (n = 991); group B: no use (n = 1119). Significant difference was observed in sperm morphology between the two groups. In the patients of group A, 68.0% of the spermatozoa featured a pathological morphology compared to only 58.1% in the subjects of group B. Patients with cell phone usage showed significantly higher T and lower LH levels than those who did not use cell phone. No significant difference between the two groups was observed regarding FSH and PRL values. Our results showed that cell phone use negatively affects sperm quality in men. Further studies with a careful design are needed to determine the effect of cell phone use on male fertility.

**Hardell L, Carlberg M, Ohlson CG, Westberg H, Eriksson M, Hansson Mild K (2007) Use of cellular and cordless telephones and risk of testicular cancer. *International Journal of Andrology* 30(2):115-22.**

A case-control study on testicular cancer included use of cellular and cordless telephones. The results were based on answers from 542 (92%) cases with seminoma, 346 (89%) with non-seminoma, and 870 (89%) controls. Regarding seminoma the use of analog cellular phones gave odds ratio (OR) = 1.2, 95% confidence interval (CI) = 0.9-1.6, digital phones OR = 1.3, CI = 0.9-1.8, and cordless phones OR = 1.1, CI = 0.8-1.5. The corresponding results for non-seminoma were OR = 0.7, CI = 0.5-1.1, OR = 0.9, CI = 0.6-1.4, and OR = 1.0, CI = 0.7-1.4, respectively. There was no dose-response effect and OR did not increase with latency time. No association was found with place of keeping the mobile phone during standby, such as trousers pocket. Cryptorchidism was associated both with seminoma (OR = 4.2, CI = 2.7-6.5) and non-seminoma (OR = 3.3, CI = 2.0-5.6), but no interaction was found with the use of cellular or cordless telephones.

**Irgens A, Kruger K, Ulstein M. (1999) The effect of male occupational exposure in infertile couples in Norway. *Journal of Occupational and Environmental Medicine* 41(12):1116-1120.**

The objective of the study was to assess whether reduced semen quality in infertile couples is associated with occupational exposures known to be hazardous to fertility. Results of the first semen analysis were linked to occupational exposure data from a self-administered questionnaire. Reduced semen quality was found in men exposed to electromagnetic fields (odds ratio, 3.22; confidence interval, 1.46 to 7.09). A tendency toward reduced semen quality was seen in commuters (OR, 1.52; CI, 0.89 to 2.59), shift workers (OR, 1.46; CI, 0.89 to 2.40), and men exposed to heavy metals (OR, 1.47; CI, 0.76 to 2.87). In general, the impact of occupational

exposure on semen quality in infertile couples in Norway seemed to be minor. However, occupational exposure mapping is still important in individual infertility investigations.

**Kesari KK, Kumar S, Behari J (2011) Effects of radiofrequency electromagnetic wave exposure from cellular phones on the reproductive pattern in male Wistar rats. *Applied Biochemistry and Biotechnology* 164(4):546-59.**

The present study investigates the effect of free radical formation due to mobile phone exposure and effect on fertility pattern in 70-day-old male Wistar rats (sham exposed and exposed). Exposure took place in Plexiglas cages for 2 h a day for 35 days to mobile phone frequency. The specific absorption rate was estimated to be 0.9 W/kg. An analysis of antioxidant enzymes glutathione peroxidase ( $P < 0.001$ ) and superoxide dismutase ( $P < 0.007$ ) showed a decrease, while an increase in catalase ( $P < 0.005$ ) was observed. Malondialdehyde ( $P < 0.003$ ) showed an increase and histone kinase ( $P = 0.006$ ) showed a significant decrease in the exposed group. Micronuclei also show a significant decrease ( $P < 0.002$ ) in the exposed group. A significant change in sperm cell cycle of G(0)-G(1) ( $P = 0.042$ ) and G(2)/M ( $P = 0.022$ ) were recorded. Generation of free radicals was recorded to be significantly increased ( $P = 0.035$ ). Our findings on antioxidant, malondialdehyde, histone kinase, micronuclei, and sperm cell cycle are clear indications of an infertility pattern, initiated due to an overproduction of reactive oxygen species. It is concluded that radiofrequency electromagnetic wave from commercially available cell phones might affect the fertilizing potential of spermatozoa.

**Kilgallon SJ, Simmons LW (2005) Image content influences men's semen quality. *Biology Letters* 1(3):253-5.**

There is increasing evidence from non-human animals that males adjust their ejaculate expenditure according to the risk of sperm competition. In this study we show that, after controlling for lifestyle factors known to influence semen quality, human males viewing images depicting sperm competition had a higher percentage of motile sperm in their ejaculates. Many lifestyle variables were confirmed to influence semen quality, including the recent suggestion that storage of mobile phones close to the testes can decrease semen quality.

**(Kim YW, Kim HS, Lee JS, Kim YJ, Lee SK, Seo JN, Jung KC, Kim N, Gimm YM.)  
Kim YW, Kim HS, Lee JS, et al. (2009) Effects of 60 Hz 14 microT magnetic field on the apoptosis of testicular germ cell in mice. *Bioelectromagnetics* 30(1):66-72.**

We recently reported that continuous exposure, for 8 weeks, of extremely low frequency (ELF) magnetic field (MF) of 0.1 or 0.5 mT might induce testicular germ cell apoptosis in BALB/c mice. In that report, the ELF MF exposure did not significantly affect the body weight or testicular weight, but significantly increased the incidence of testicular germ cell death. In the present study, we aimed to further characterize the effect of a 16-week continuous exposure to ELF MF of 14 or 200 microT on testicular germ cell apoptosis in mice. There were no significant effects of MF on body weight and testosterone levels in mice. In TUNEL staining (In situ terminal deoxynucleotidyl transferase-mediated deoxy-UTP nick end labeling), germ cells showed a significantly higher apoptotic rate in exposed mice than in sham controls ( $P < 0.001$ ). TUNEL-positive cells were mainly spermatogonia. In an electron microscopic study, degenerating spermatogonia showed condensation of nuclear chromatin similar to apoptosis. These results indicate that apoptosis may be induced in spermatogenic cells in mice by continuous exposure to 60 Hz MF of 14 microT.

**Koldayev VM, Shchepin YV. (1997) Effects of electromagnetic radiation on embryos of sea-urchins. *Bioelectrochemistry and Bioenergetics* 43:161-164.**

Electromagnetic radiation (EMR) causes a decrease in the number of fertilized eggs and an increase in the number of zygotes with abnormal fertilization envelopes in sea-urchins. The microstructural impairments of the cellular surface, the increase of lipid peroxidation and the changes of amino acid

metabolism show that the impairments of the development of embryos exposed to EMR are caused by the damages of the membrane structures.

**Kubinyi G, Thuroczy G, Bakos J, Boloni E, Sinay H, Szabo LD.(1996) Effect of continuous-wave and amplitude-modulated 2.45 GHz microwave radiation on the liver and brain aminoacyl-transfer RNA synthetases of in utero exposed mice. Bioelectromagnetics 17(6):497-503.**

Investigations have been carried out concerning the effects of microwave (MW) exposure on the aminoacyl-transfer ribonucleic acid (tRNA) synthetase of the progeny of females that were exposed during their entire period of gestation (19 days). The changes caused by continuous-wave (CW) and amplitude-modulated (AM) MW radiation have been compared. CFLP mice were exposed to MW radiation for 100 min each day in an anechoic room. The MW frequency was 2.45 GHz, and the amplitude modulation had a 50 Hz rectangular waveform (on/off ratio, 50/50%). The average power density exposure was 3 mW/cm<sup>2</sup>, and the whole body specific absorption rate (SAR) was 4.23 +/- 0.63 W/kg. The weight and mortality of the progeny were followed until postnatal day 24. Aminoacyl-tRNA synthetase enzymes and tRNA from the brains and livers of the offspring (461 exposed, 487 control) were isolated. The aminoacyl-tRNA synthetase activities were determined. The postnatal increase of body weight and organ weight was not influenced by the prenatal MW radiation. The activity of enzyme isolated from the brain showed a significant decrease after CW MW exposure, but the changes were not significant after 50 Hz AM MW exposure. The activity of the enzyme isolated from liver increased under CW and 50 Hz modulated MW.

**Khurana VG, Teo C, Bittar RG. (2009) Health risks of cell phone technology. Surgical Neurology 72(4):436-7; author reply 437.**

**Comment on Pawl R. (2008) Cell phones more dangerous than cigarettes! Surgical Neurology 70(5):445-6.**

Dear Editor:

The editorial by Dr Pawl [12] is timely and discusses an emerging public health concern. This reignited debate [9] has not escaped the attention of the US Congress, whose Subcommittee on Domestic Policy chaired by Congressman Dennis Kucinich held a landmark hearing regarding this topic on September 25, 2008 [7]. The proposed health ramifications of ubiquitous and chronic immersion in the electromagnetic fields (EMFs) of cell phones and transmission masts are not only limited to brain tumors but also include salivary gland tumors [13], male infertility [1,5], behavioral disturbances [4], and electrohypersensitivity (previously "microwave sickness syndrome") [10]. Since the publication of the seminal BioInitiative Report [2] in August 2007 by a multinational group of recognized scientists, physicians, and policy makers, important steps have been taken in many countries [8], urging evidence-based precaution as compelling new long-term epidemiologic data accrue from the Hardell group and World Health Organization-administered INTERPHONE consortium [6]. It is recommended that serial age-adjusted primary central nervous system tumor incidence rates from databases, such as those of the Central Brain Tumor Registry of the United States [3], be carefully followed in time for trends. Although there is no currently proven mechanism via which cell phone radiation can cause neoplasia, it is notable that there are more than one dozen peer-reviewed papers from laboratories in at least 7 countries including the United States showing that cell phone or similar low-intensity EMFs can break DNA or modulate it structurally [11], despite comments stating otherwise [14]. A simple precautionary step includes using a landline in preference to a cell phone whenever possible. If talking on a cell phone, a wired earpiece or speaker-phone mode should be used to increase the distance between the antenna (external or concealed) and the user's head. Restricting children's cell phone usage should also be strongly considered given the recent testimony of Dr Ronald Herberman and Dr David Carpenter [7].

January 2, 2012

Cindy Sage, Sage Associates, CHE-EMF

Vini G. Khurana, MBBS, PhD, FRACS

The Canberra Hospital, Canberra, Australia

Charles Teo, MBBS, FRACS, Prince of Wales Private Hospital, New South Wales, Australia

Richard G. Bittar, MBBS, PhD, FRACS, Royal Melbourne Hospital and The Alfred Hospital  
Victoria, Australia

#### References

- [1] Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. *Fertil Steril* 2008;89: 124-8.
- [2] BioInitiative Working Group (2007). BioInitiative report: a rationale for a biologically-based public exposure standard for electromagnetic fields (ELF and RF). Sage C., Carpenter D.O., eds. (<http://www.bioinitiative.org>).
- [3] CBTRUS. Statistical Reports (2002-3, 2004-5, 2005-6, 2007-8). Primary Brain Tumors in the United States, 1995–2004 (years of data collected in sequential reports). Central Brain Tumor Registry of the United States (<http://cbtrus.org/reports/reports.html>).
- [4] Divan HA, Kheifets L, Obel C, Olsen J. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. *Epidemiology* 2008;19:523-9.
- [5] Eroglu O, Oztas E, Yildirim I, Kir T, Aydur E, Komesli G, et al. Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study. *Arch Med Res* 2006;37: 840-3.
- [6] Hardell L, Carlberg M, Soderqvist F, Hansson Mild K. Meta-analysis of long-term mobile phone users and the association with brain tumours. *Int J Oncol* 2008;32:1097-103.
- [7] <http://domesticpolicy.oversight.house.gov/story.asp?ID=2199>.
- [8] <http://www.brain-surgery.us/Internationalsteps.html>.
- [9] <http://www.brain-surgery.us/NYTimes.pdf>.
- [10] Hutter HP, Moshhammer H, Wallner P, Kundi M. Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. *Occup Environ Med* 2006; 63:307-13.
- [11] Microwave News (L. Slesin, Editor). "Sweeping...and wrong"  
[Response to Vogel G. Fraud charges cast doubt on claims of DNA damage from cell phone fields. *Science* 2008;321:1144-1145]. <http://www.microwavenews.com> (posted September 3, 2008).
- [12] Pawl R. Cell phones more dangerous than cigarettes! *Surg Neurol* 2008;70:445-56 [Editorial].
- [13] Sadetzki S, Chetrit A, Jarus-Hakak A, Cardis E, Deutch Y, Duvdevani S, et al. Cellular phone use and risk of benign and malignant parotid gland tumors—a nationwide case-control study. *Am J Epidemiol* 2008; 167:457-67.

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

*Surgical Neurology* xx (2009) xxx

[www.surgicalneurology-online.com](http://www.surgicalneurology-online.com)

0090-3019/\$ – see front matter © 2009 Published by Elsevier Inc.

doi:10.1016/j.surneu.2008.11.013

ARTICLE IN PRESS

January 2, 2012

Cindy Sage, Sage Associates, CHE-EMF

[14] Vogel G. Fraud charges cast doubt on claims of DNA damage from cell phone fields. *Science* 2008;321:1144-5.

Commentary

Obviously, I cannot agree with Dr Khurana more. His cautions are in line with my own, as stated in the referenced editorial. He is one of the finders; I am just a messenger. Hopefully, the committee action initiated by Congressman Kucinich will lead to appropriate further research and regulatory changes as needed.

Ron Pawl, MD

Department of Neurosurgery

University of Illinois

Lake Forest, IL 60045, USA

ARTICLE IN PRESS

**Larsen AI, Olsen J, Svane O. (1991) Gender-specific reproductive outcome and exposure to high-frequency electromagnetic radiation among physiotherapists. *Scandinavian Journal of Work and Environmental Health* 17(5):324-329.**

The aim of this case-referent study was to investigate reproductive hazards other than congenital malformations after exposure to high-frequency electromagnetic radiation. Cases and referents were sampled from a cohort of pregnancies of members of the Union of Danish Physiotherapists through linkage of the union file with national medical registers. Case groups were spontaneous abortions and children with low birth-weight prematurity, and stillbirth/death within one year. Exposure to high-frequency electromagnetic radiation before and during pregnancy was assessed through telephone interviews. As referents to the 270 cases, 316 pregnancies were randomly sampled. A total of 8.4% did not participate. Only 23.5% of the children born by the highly exposed mothers were boys. This value is a statistically significantly altered gender ratio showing a dose-response pattern. High-frequency electromagnetic radiation was furthermore associated with low birthweight, but only for male newborns. The other outcomes were not statistically significantly associated with exposure to high-frequency electromagnetic radiation.

**La Vignera S, Condorelli RA, Vicari E, D'Agata R, Calogero AE (2011) Effects of the exposure to mobile phones on male reproduction: a review of the literature. *Journal of Andrology* Jul 28. [Epub ahead of print]**

The use of mobile phones is now widespread. A great debate is going on about the possible damage that the radiofrequency electromagnetic radiation (RF-EMR) emitted by mobile phones exerts on different organs and apparatuses. Aim of this article was to review the existing literature exploring the effects of RF-EMR on the male reproductive function in experimental animals and human beings. Studies on the experimental animals have been conducted in rats, mice, and rabbits using a similar design based upon mobile phone radiofrequency exposure for a variable length of time. Altogether the results of these studies show that RF-EMR decreases sperm count and motility, and increases the oxidative stress. In human beings, two different experimental approaches have been followed, one has explored the effects of RF-EMR directly on spermatozoa and the other has evaluated the sperm parameters in men using or not mobile phones. The results show that human spermatozoa exposed to RF-EMR have decreased motility, morphometric abnormalities, and increased oxidative stress, whereas men using mobile phones have decreased sperm concentration, motility (particularly the rapid progressive one), normal morphology, and viability. These abnormalities seem to be directly related with the length of mobile phone use.

**Lee GM, Neutra RR, Hristova L, Yost M, Hiatt RA (2002) A nested case-control study of residential and personal magnetic field measures and miscarriages. *Epidemiology* 13(1):21-31. Erratum in *Epidemiology* 2003 4(2):255.**

January 2, 2012

Cindy Sage, Sage Associates, CHE-EMF

We conducted a nested case-control study (177 cases, 550 controls) to assess the relation between retrospective magnetic field measures and clinical miscarriage among members of the northern California Kaiser Permanente medical care system. We also conducted a prospective substudy of 219 participants of the same parent cohort to determine whether 12-week and 30-week exposure assessments were similar. We evaluated wire codes, area measures, and three personal meter metrics: (1) the average difference between consecutive levels (a rate-of-change metric), (2) the maximum level, and (3) the time-weighted average. For wire codes and area measures we found little association. For the personal metrics (30 weeks after last menstrual period), we found positive associations. Each exposure was divided into quartiles, with the lowest quartile as referent. Starting with the highest quartile, adjusted odds ratios and 95% confidence intervals were 3.1 (95% CI = 1.6-6.0), 2.3 (95% CI = 1.2-4.4), and 1.5 (95% CI = 0.8-3.1) for the rate-of-change metric; 2.3 (95% CI = 1.2-4.4), 1.9 (95% CI = 1.0-3.5), and 1.4 (95% CI = 0.7-2.8) for the maximum value; and 1.7 (95% CI = 0.9-3.3), 1.7 (95% CI = 0.9-3.3), and 1.7 (95% CI = 0.9-3.3) for the time-weighted average. The odds ratio conveyed by being above a 24-hour time-weighted average of 2 milligauss was 1.0 (95% CI = 0.5-2.1). Exposure assessment measurements at 12 weeks were poorly correlated with those taken at 30 weeks. Nonetheless, the prospective substudy results regarding miscarriage risk were consistent with the nested study results.

Comment in

- Epidemiology. 2002 Jan;13(1):1-4.
- Epidemiology. 2002 Mar;13(2):237-8.
- Epidemiology. 2002 May;13(3):372.

**Lee JW, Kim KS, Lee SM, Eom SJ, Troitsky RV (2002) A novel design of thermal anomaly for mammary gland tumor phantom for microwave radiometer. IEEE Transactions on Bio-medical Engineering 49(7):694-9.**

Microwave radiometry is the spectral measurement technique of resolving electromagnetic radiation of all matters which temperature is above absolute zero. This technique utilizes the electromagnetic noise field generated by a thermal volume similar to a mechanism existing in biological tissues. One particular application of microwave radiometry is for analyzing temperature differentials of inside of human body to detect and diagnose some crucial pathological conditions. For the general evaluation of a microwave radiometer, we propose a new type of phantom containing a mammary gland tumor imitator by considering biological heat diffusion effects propagated by a real tumor. Theoretical researches of human tumor revealed the fact that temperature distribution of tissues around a tumor formed a Gaussian statistics. To comply with the physiological property of the real tumor, we built a mammary gland tumor imitator composed of two parts (pseudotumor and thermal anomaly) and observed its temperature distribution when it was placed inside a phantom. Our results showed that the thermal properties of tumor imitator well agreed with heat-transfer properties of a real tumor and the proportional linear relationship existed between the location of tumor imitator and the intensity of radiometer measurements. From this relationship, we could also estimate several parameters related with our phantom, such as the minimum detectable size and maximum detectable depth of a tumor imitator.

**Li DK, Yan B, Li Z, Gao E, Miao M, Gong D, Weng X, Ferber JR, Yuan W (2010) Exposure to magnetic fields and the risk of poor sperm quality. Reproductive Toxicology 29(1):86-92.**

We conducted a population-based case-control study among healthy sperm donors to study exposure to magnetic fields (MFs) and poor sperm quality. All participants wore a meter to capture daily MF exposure. After controlling for confounders, compared to those with lower MF exposure, those whose 90th percentile MF level  $\geq 1.6$  mG had a two-fold increased risk of abnormal sperm motility and morphology (odds ratio (OR): 2.0, 95% confidence interval (CI): 1.0-3.9). Increasing duration of MF exposure above 1.6 mG further increased the risk ( $p=0.03$  for trend test). Importantly, the association and dose-response relationship were strengthened when restricted to those whose measurement day reflected their typical day of the previous 3 months (a likely period of spermatogenesis). Age-adjusted Spearman Rank Order Correlations showed an inverse

correlation between MF exposure and all semen parameters. Our study provides some evidence for the first time that MF exposure may have an adverse effect on sperm quality.

**Magras IN, Xenos TD (1997) RF radiation-induced changes in the prenatal development of mice. Bioelectromagnetics 18(6):455-61.**

The possible effects of radiofrequency (RF) radiation on prenatal development has been investigated in mice. This study consisted of RF level measurements and in vivo experiments at several places around an "antenna park." At these locations RF power densities between 168 nW/cm<sup>2</sup> and 1053 nW/cm<sup>2</sup> were measured. Twelve pairs of mice, divided in two groups, were placed in locations of different power densities and were repeatedly mated five times. One hundred eighteen newborns were collected. They were measured, weighed, and examined macro- and microscopically. A progressive decrease in the number of newborns per dam was observed, which ended in irreversible infertility. The prenatal development of the newborns, however, evaluated by the crown-rump length, the body weight, and the number of the lumbar, sacral, and coccygeal vertebrae, was improved.

**Mailankot M, Kunnath AP, Jayalekshmi H, Koduru B, Valsalan R. Radio frequency electromagnetic radiation (RF-EMR) from GSM (0.9/1.8GHz) mobile phones induces oxidative stress and reduces sperm motility in rats. Clinics (Sao Paulo). 2009;64(6):561-5.**

**INTRODUCTION:** Mobile phones have become indispensable in the daily lives of men and women around the globe. As cell phone use has become more widespread, concerns have mounted regarding the potentially harmful effects of RF-EMR from these devices.

**OBJECTIVE:** The present study was designed to evaluate the effects of RF-EMR from mobile phones on free radical metabolism and sperm quality.

**MATERIALS AND METHODS:** Male albino Wistar rats (10-12 weeks old) were exposed to RF-EMR from an active GSM (0.9/1.8 GHz) mobile phone for 1 hour continuously per day for 28 days. Controls were exposed to a mobile phone without a battery for the same period. The phone was kept in a cage with a wooden bottom in order to address concerns that the effects of exposure to the phone could be due to heat emitted by the phone rather than to RF-EMR alone. Animals were sacrificed 24 hours after the last exposure and tissues of interest were harvested.

**RESULTS:** One hour of exposure to the phone did not significantly change facial temperature in either group of rats. No significant difference was observed in total sperm count between controls and RF-EMR exposed groups. However, rats exposed to RF-EMR exhibited a significantly reduced percentage of motile sperm. Moreover, RF-EMR exposure resulted in a significant increase in lipid peroxidation and low GSH content in the testis and epididymis.

**CONCLUSION:** Given the results of the present study, we speculate that RF-EMR from mobile phones negatively affects semen quality and may impair male fertility.

**Makker K, Varghese A, Desai NR, Mouradi R, Agarwal A. (2009) Cell phones: modern man's nemesis? Reprod Biomed Online. 2009 Jan;18(1):148-57.**

Over the past decade, the use of mobile phones has increased significantly. However, with every technological development comes some element of health concern, and cell phones are no exception. Recently, various studies have highlighted the negative effects of cell phone exposure on human health, and concerns about possible hazards related to cell phone exposure have been growing. This is a comprehensive, up-to-the-minute overview of the effects of cell phone exposure on human health. The types of cell phones and cell phone technologies currently used in the world are discussed in an attempt to improve the understanding of the technical aspects, including the effect of cell phone exposure on the cardiovascular system, sleep and cognitive function, as well as localized and general adverse effects, genotoxicity potential, neurohormonal secretion and tumour induction. The proposed mechanisms by which cell phones adversely affect various aspects of human health, and male fertility in particular, are explained, and the emerging molecular techniques



and approaches for elucidating the effects of mobile phone radiation on cellular physiology using high-throughput screening techniques, such as metabolomics and microarrays, are discussed. A novel study is described, which is looking at changes in semen parameters, oxidative stress markers and sperm DNA damage in semen samples exposed in vitro to cell phone radiation.

**Moskowitz JM (2011) Research on the effects of cell phone radiation on human sperm.**

**CEAC. Available at:**

**[http://www.ci.berkeley.ca.us/uploadedFiles/Planning\\_and\\_Development/Level\\_3\\_-\\_Commissions/Commission\\_for\\_Community\\_Environmental\\_Advisory/CEAC2011-04-07\\_1i-Effects\\_of\\_CellPhoneRadiation\\_onHumanSperm-Moskowitz.pdf](http://www.ci.berkeley.ca.us/uploadedFiles/Planning_and_Development/Level_3_-_Commissions/Commission_for_Community_Environmental_Advisory/CEAC2011-04-07_1i-Effects_of_CellPhoneRadiation_onHumanSperm-Moskowitz.pdf)**

The following terms were used in a PubMed search: (cell or mobile) phone sperm. Fourteen English-language, papers were found that examined the effects of cell phone radiation on human sperm including nine original studies and five review papers. Eight of the nine original studies reported adverse effects of cell phone radiation on at least one of four outcomes: sperm count (C), motility (M), viability (V) or morphology (S). The adverse effects obtained in these studies were as follows: C/M/V/S (Agarwal et al., 2008a); M/V (Agarwal et al., 2009; De luliis et al., 2009); M/S (Wdowiak et al., 2007); M (Erogul et al., 2006; Fejes et al., 2005); and S (Falzone et al., 2008; Falzone et al., 2011). The ninth study examined sperm for signs of pre-apoptosis but found no evidence for this mechanism (Falzone et al., 2010). Cell phone radiation was associated with decreased sperm motility (M) in six of the eight studies that assessed this outcome. The next most commonly observed effect was reduced viability (V) in three studies. Note that not all studies measured each of these four outcomes. The research abstracts from the search follow. The original studies are in the first section followed by the review papers. The abstracts are listed in alphabetical order by first author.

**Nakamura H, Nagase H, Ogino K, Hatta K, Matsuzaki I. (2000) Uteroplacental circulatory disturbance mediated by prostaglandin F(2alpha) in rats exposed to microwaves. Reproductive Toxicology 14(3):235-240.**

To clarify the effects of microwaves on pregnancy, uterine or uteroplacental blood flow and endocrine and biochemical mediators, including corticosterone, estradiol, prostaglandin E(2) (PGE(2)), and prostaglandin F(2)alpha (PGF(2)alpha), were measured in rats exposed to continuous-wave (CW) microwave at 2 mW/cm(2) incident power density at 2450 MHz for 90 min. Colonic temperature in virgin and pregnant rats was not significantly altered by microwave treatment. Microwaves decreased uteroplacental blood flow and increased progesterone and PGF(2)alpha in pregnant, but not in virgin rats. Intraperitoneal (i.p.) administration of angiotensin II, a uteroplacental vasodilator, before microwave exposure prevented the reduction in uteroplacental blood flow and the increased progesterone and PGF(2)alpha in pregnant rats. Increased corticosterone and decreased estradiol during microwave exposure were observed independent of pregnancy and pretreatment with angiotensin II. These results suggest that microwaves (CW, 2 mW/cm(2), 2450 MHz) produce uteroplacental circulatory disturbances and ovarian and placental dysfunction during pregnancy, probably through nonthermal actions. The uteroplacental disturbances appear to be due to actions of PGF(2)alpha and may pose some risk for pregnancy.

**Otitoloju AA, Obe IA, Adewale OA, Otubanjo OA, Osunkalu VO (2010) Preliminary study on the induction of sperm head abnormalities in mice, *Mus musculus*, exposed to radiofrequency radiations from global system for mobile communication base stations. Bulletin of Environmental Contamination and Toxicology 84(1):51-4.**

The exposure of male mice to radiofrequency radiations from mobile phone (GSM) base stations at a workplace complex and residential quarters caused 39.78 and 46.03%, respectively, in sperm head abnormalities compared to 2.13% in control group. Statistical analysis of sperm head abnormality score showed that there was a significant ( $p < 0.05$ ) difference in occurrence of sperm head abnormalities in test animals. The major abnormalities observed were knobbed hook, pin-head and

banana-shaped sperm head. The occurrence of the sperm head abnormalities was also found to be dose dependent. The implications of the observed increase occurrence of sperm head abnormalities on the reproductive health of humans living in close proximity to GSM base stations were discussed.

**Panagopoulos DJ, Karabarbounis A, Margaritis LH (2004) Effect of GSM 900-MHz mobile phone radiation on the reproductive capacity of *Drosophila melanogaster* Electromagnetic biology and medicine 23:29-43.**

Pulsed radio frequency, (RF), electromagnetic radiation from common GSM mobile phones, (Global System for Mobile Telecommunications) with a carrier frequency at 900 MHz, “modulated” by human voice, (speaking emission) decreases the reproductive capacity of the insect *Drosophila melanogaster* by 50%–60%, whereas the corresponding “nonmodulated” field (nonspeaking emission) decreases the reproductive capacity by 15%–20%. The insects were exposed to the near field of the mobile phone antenna for 6 min per day during the first 2–5 days of their adult lives. The GSM field is found to affect both females and males. Our results suggest that this field-radiation decreases the rate of cellular processes during gonad development in insects.

**Panagopoulos DJ, Margaritis LH (2008) Mobile telephony radiation effects on living organisms. In: Harper AC, Buress RV, eds. Mobile Telephones. Nova Science Publishers, Inc: 107-49.**

A number of serious non thermal biological effects, ranging from changes in cellular function like proliferation rate changes or gene expression changes to cell death induction, decrease in the rate of melatonin production and changes in electroencephalogram patterns in humans, population declinations of birds and insects, and small but statistically significant increases of certain types of cancer, are attributed in our days to the radiations emitted by mobile telephony antennas of both handsets and base stations. This chapter reviews briefly the most important experimental, clinical and statistical findings and presents more extensively a series of experiments, concerning cell death induction on a model biological system. Mobile telephony radiation is found to decrease significantly and non-thermally insect reproduction by up to 60%, after a few minutes daily exposure for only few days. Both sexes were found to be affected. The effect is due to DNA fragmentation in the gonads caused by both types of digital mobile telephony radiation used in Europe, GSM 900MHz, (Global System for Mobile telecommunications), and DCS 1800MHz, (Digital Cellular System). GSM was found to be even more bioactive than DCS, due to its higher intensity under equal conditions. The decrease in reproductive capacity seems to be non-linearly depended on radiation intensity, exhibiting a peak for intensities higher than 200  $\mu\text{W}/\text{cm}^2$  and an intensity “window” around 10  $\mu\text{W}/\text{cm}^2$  where it becomes maximum. In terms of the distance from a mobile phone antenna, the intensity of this “window” corresponds under usual conditions to a distance of 20-30 cm. The importance of different parameters of the radiation like intensity, carrier frequency and pulse repetition frequency, in relation to the recorded effects are discussed. Finally, this chapter describes a plausible biophysical and biochemical mechanism which can explain the recorded effects of mobile telephony radiations on living organisms.

**Peyman A, Khalid M, Calderon C, Addison D, Mee T, Maslanyj M, Mann S. (2011) Assessment of exposure to electromagnetic fields from wireless computer networks (wi-fi) in schools; results of laboratory measurements. Health Phys. 100(6):594-612.**

Laboratory measurements have been carried out with examples of Wi-Fi devices used in UK schools to evaluate the radiofrequency power densities around them and the total emitted powers. Unlike previous studies, a 20 MHz bandwidth signal analyzer was used, enabling the whole Wi-Fi signal to be captured and monitored. The radiation patterns of the laptops had certain similarities, including a minimum toward the torso of the user and two maxima symmetrically opposed across a vertical plane bisecting the screen and keyboard. The maxima would have resulted from separate antennas mounted behind the top left and right corners of the laptop screens. The patterns for access points were more symmetrical with generally higher power densities at a given distance. The

spherically-integrated radiated power (IRP) ranged from 5 to 17 mW for 15 laptops in the 2.45 GHz band and from 1 to 16 mW for eight laptops in the 5 GHz band. For practical reasons and because access points are generally wall-mounted with beams directed into the rooms, their powers were integrated over a hemisphere. These ranged from 3 to 28 mW for 12 access points at 2.4 GHz and from 3 to 29 mW for six access points at 5 GHz. In addition to the spherical measurements of IRP, power densities were measured at distances of 0.5 m and greater from the devices, and consistent with the low radiated powers, these were all much lower than the ICNIRP reference level.

**Pyrpasopoulou A, Kotoula V, Cheva A, Hytioglou P, Nikolakaki E, Magras IN, Xenos TD, Tsiboukis TD, Karkavelas G. (2004) Bone morphogenetic protein expression in newborn rat kidneys after prenatal exposure to radiofrequency radiation. *Bioelectromagnetics* 25(3):216-227.**

Effects of nonthermal radiofrequency radiation (RFR) of the global system of mobile communication (GSM) cellular phones have been as yet mostly studied at the molecular level in the context of cellular stress and proliferation, as well as neurotransmitter production and localization. In this study, a simulation model was designed for the exposure of pregnant rats to pulsed GSM-like RFR (9.4 GHz), based on the different resonant frequencies of man and rat. The power density applied was 5 microW/cm<sup>2</sup>, in order to avoid thermal electromagnetic effects as much as possible. Pregnant rats were exposed to RFR during days 1-3 postcoitum (p.c.) (embryogenesis, pre-implantation) and days 4-7 p.c. (early organogenesis, peri-implantation). Relative expression and localization of bone morphogenetic proteins (BMP) and their receptors (BMPR), members of a molecular family currently considered as major endocrine and autocrine morphogens and known to be involved in renal development, were investigated in newborn kidneys from RFR exposed and sham irradiated (control) rats. Semi-quantitative duplex RT-PCR for BMP-4, -7, BMPR-IA, -IB, and -II showed increased BMP-4 and BMPR-IA, and decreased BMPR-II relative expression in newborn kidneys. These changes were statistically significant for BMP-4, BMPR-IA, and -II after exposure on days 1-3 p.c. ( $P < .001$  each), and for BMP-4 and BMPR-IA after exposure on days 4-7 p.c. ( $P < .001$  and  $P = .005$ , respectively). Immunohistochemistry and in situ hybridization (ISH) showed aberrant expression and localization of these molecules at the histological level. Our findings suggest that GSM-like RFR interferes with gene expression during early gestation and results in aberrations of BMP expression in the newborn. These molecular changes do not appear to affect renal organogenesis and may reflect a delay in the development of this organ. The differences of relative BMP expression after different time periods of exposure indicate the importance of timing for GSM-like RFR effects on embryonic development.

**Redmayne M, Smith E, Abramson MJ (2011) Adolescent in-school cellphone habits: a census of rules, survey of their effectiveness, and fertility implications. *Reproductive Toxicology* 32:354-9.**

We explored school cellphone rules and adolescent exposure to cellphone microwave emissions during school with a census and survey respectively. The data were used to assess health and policy implications through a review of papers assessing reproductive bio-effects after exposure to cellphone emissions, this being most relevant to students' exposure. All schools banned private use of cellphones in class. However, 43% of student participants admitted breaking this rule. A high-exposure group of risk-takers was identified for whom prohibited in-school use was positively associated with high texting rates, carrying the phone switched-on >10 hours/day, and in-pocket use. The fertility literature is inconclusive, but increasingly points towards significant time- and dose- dependent deleterious effects from cellphone exposure on sperm. Genotoxic effects have been demonstrated from „non-thermal exposures, but not consistently. There is sufficient evidence and expert opinion to warrant an enforced school policy removing cellphones from students during the day.

**Sage C, Johansson O, Sage SA (2007) Personal digital assistant (PDA) cell phone units produce elevated extremely-low frequency electromagnetic field emissions. *Bioelectromagnetics* 28(5):386-92.**

Initial tests indicate that personal and occupational use of personal digital assistants (PDAs or palm-held wireless units) produce high intensity bursts of extremely-low frequency electromagnetic fields (ELF-EMF). These emissions could result in comparatively high ELF-EMF exposure in persons that carry a PDA close to the body (i.e., in a pocket or on a belt); or held to the head for cell phone conversations. ELF-EMF emissions of 10 microT were recorded on PDAs during normal office use over a 24 h test period. Results of ELF-EMF measurements show that email transmit and receive functions produce rapid, short-duration ELF-EMF spikes in the 2-10 microT range, each lasting several seconds to over a minute apparently depending on file download size. Some units produced spikes as high as 30-60 microT during email activities. Cell phone activity on PDAs produced continuously elevated ELF-EMF readings in the 0.5-1 microT range, as opposed to the rapid spiking pattern for email receipt and transmission. Switching the PDA unit from "OFF" to "ON" position resulted in single ELF-EMF pulses of over 90 microT on two units. Email downloads into the PDA can occur randomly throughout the day and night when the unit is "ON"; thus the user who wears the PDA may be receiving high-intensity ELF-EMF pulses throughout the day and night. The frequency of email traffic on the PDA, and the power switching unit (battery unit) may affect the frequency and intensity of ELF-EMF emissions.

**Salama N, Kishimoto T, Kanayama HO (2010) Effects of exposure to a mobile phone on testicular function and structure in adult rabbit. International Journal of Andrology 33(1):88-94. Comment in: International Journal of Andrology 33(1):95; author reply 96-7.**

The accumulating effects of exposure to electromagnetic radiation emitted by a conventional mobile phone (standby position) on the testicular function and structure are not yet fully investigated. To study these effects longitudinally, a total of 24 adult male rabbits were randomly and equally divided into three groups. Rabbits in the first (phone) group were exposed, in specially designed cages, to radio frequency emitted from the mobile phone (800 MHz) in a standby position opposite to that of testes for 8 h daily for 12 weeks. The second group consisted of the stress controls which were kept in the same kind of cages to appreciate any cage-induced anxiety. The third group included the ordinary controls which were kept in the conventional roomy cages. Semen analysis and sperm function tests (viability, hypo-osmotic swelling and acridine orange) were conducted weekly. Histological testicular sections and serum total testosterone were also evaluated. A drop in the sperm concentration appeared in the phone group at week 6. This became statistically significant at week 8, compared with the two control (stress and ordinary) groups (133, 339 and 356 x 10<sup>6</sup>/mL, respectively) and to the initial sperm count (341 x 10<sup>6</sup>/mL) of this group. Motile sperm population showed similarity amongst the three study groups until week 10 when it declined significantly, and thereafter in the phone and stress control groups, with more significant decline in the phone animals (50, 61 and 72.4%, respectively). Histological examination showed also a significant decrease in the diameter of seminiferous tubules in the phone group vs. the stress and ordinary controls (191 microm vs. 206 and 226 microm, respectively). The other study points did not show any difference. In conclusion, low intensity pulsed radio frequency emitted by a conventional mobile phone kept in the standby position could affect the testicular function and structure in the adult rabbit.

**Sheynkin Y, Jung M, Yoo P, Schulsinger D, Komaroff E (2005) Increase in scrotal temperature in laptop computer users. Human Reproduction 20(2):452-5.**

**BACKGROUND:** Scrotal hyperthermia has been identified as a risk factor for male infertility. Laptop computers (LC) have become part of a contemporary lifestyle and have gained popularity among the younger population of reproductive age. LC are known to reach high internal operating temperatures. We evaluated the thermal effect of LC on the scrotum.

**METHODS:** Right and left scrotal temperature (ScT) was measured in 29 healthy volunteers in two separate 60 min sessions. ScT was recorded from thermocouples on a digital datalogger every 3 min with the working LC in a laptop position and in the same sitting position with approximated thighs without LC.

**RESULTS:** ScT increased significantly on the right and left side in the group with working LC (2.8

degrees C and 2.6 degrees C, respectively;  $P < 0.0001$ ) and without LC (2.1 degrees C,  $P < 0.0001$ ). However, ScT elevation with working LC was significantly higher ( $P < 0.0001$ ).

**CONCLUSIONS:** Working LC in a laptop position causes significant ScT elevation as a result of heat exposure and posture-related effects. Long-term exposure to LC-related repetitive transient scrotal hyperthermia is a modern lifestyle feature that may have a negative impact upon spermatogenesis, specifically in teenage boys and young men. Further studies of such thermal effects on male reproductive health are warranted.

**Sommer AM, Grote K, Reinhardt T, Streckert J, Hansen V, Lerchl A (2009) Effects of radiofrequency electromagnetic fields (UMTS) on reproduction and development of mice: a multi-generation study. Radiation Research 171(1):89-95.**

Male and female mice (C57BL) were chronically exposed (life-long, 24 h/day) to mobile phone communication electromagnetic fields at approximately 1966 MHz (UMTS). Their development and fertility were monitored over four generations by investigating histological, physiological, reproductive and behavioral functions. The mean whole-body SARs, calculated for adult animals at the time of mating, were 0 (sham), 0.08, 0.4 and 1.3 W/kg. Power densities were kept constant for each group (0, 1.35, 6.8 and 22 W/m<sup>2</sup>), resulting in varying SARs due to the different numbers of adults and pups over the course of the experiment. The experiment was done in a blind fashion. The results show no harmful effects of exposure on the fertility and development of the animals. The number and the development of pups were not affected by exposure. Some data, albeit without a clear dose-response relationship, indicate effects of exposure on food consumption that is in accordance with some data published previously. In summary, the results of this study do not indicate harmful effects of long-term exposure of mice to UMTS over several generations.

**Stefanis P, Drakeley A, Gazvani R, Lewis-Jones Di (2006) Growing concern over the safety of using mobile phones and male fertility. Archives of Andrology 52(1):9-14**

There are growing concerns about the possible hazards of electromagnetic waves emitted by mobile phones on human health. One of the biggest concerns is their possible association with increased risk of cancer and their possible effects on cellular DNA. Electromagnetic waves can inflict their results through both thermal and non-thermal effects. There are many animal studies that show that electromagnetic waves have a wide range of damaging effects on the male reproductive system and sperm parameters. However, similar studies are quite limited in humans, and the results of animal studies should be interpreted with caution when considering their application to humans. Large controlled studies are required before confirming such possible effects on male fertility.

**Tuan Anh Vu; Uyen Dinh Nguyen. (2010) Evaluation of human testis absorption in the near field of cellular phone. Communications and Electronics (ICCE), Third International Conference on**

Due to the recent explosion of users in the area of mobile communications and, conveniently, most users place the cellular phone in the trouser's pocket. In this paper, a cellular phone antenna is placed close proximity to the trouser's pocket. Using FDTD (Finite Difference Time Domain) method and the male Visible Human model, the SAR (Specific Absorption Rate) distribution is calculated for the male testis. In addition, an attempt is made to simulate the reduction of SAR absorption by using simple grid metal covering the antenna.

**Vu TA, Nguyen UD (2010) Evaluation of human testis absorption in the near field of cellular phone. IEEE. conference paper. DOI:10.1109/ICCE.2010.5670642**

Due to the recent explosion of users in the area of mobile communications and, conveniently, most users place the cellular phone in the trouser's pocket. In this paper, a cellular phone antenna is placed close proximity to the trouser's pocket. Using FDTD (Finite Difference Time Domain)

method and the male Visible Human model, the SAR (Specific Absorption Rate) distribution is calculated for the male testis. In addition, an attempt is made to simulate the reduction of SAR absorption by using simple grid metal covering the antenna.

**Wdowiak A, Wdowiak L, Wiktor H (2007) Evaluation of the effect of using mobile phones on male fertility. *Annals of Agricultural and Environmental Medicine: AAEM* 14(1):169-72.**

The problem of the lack of offspring is a phenomenon concerning approximately 15% of married couples in Poland. Infertility is defined as inability to conceive after a year of sexual intercourses without the use of contraceptives. In half of the cases the causative factor is the male. Males are exposed to the effect of various environmental factors, which may decrease their reproductive capabilities. A decrease in male fertility is a phenomenon which occurs within years, which may suggest that one of the reasons for the decrease in semen parameters is the effect of the development of techniques in the surrounding environment. A hazardous effect on male fertility may be manifested by a decrease in the amount of sperm cells, disorders in their mobility, as well as structure. The causative agents may be chemical substances, ionizing radiation, stress, as well as electromagnetic waves. The objective of the study was the determination of the effect of the usage of cellular phones on the fertility of males subjected to marital infertility therapy. The following groups were selected from among 304 males covered by the study: Group A: 99 patients who did not use mobile phones, Group B: 157 males who have used GSM equipment sporadically for the period of 1-2 years, and Group C: 48 people who have been regularly using mobile phone for more than 2 years. In the analysis of the effect of GSM equipment on the semen it was noted that an increase in the percentage of sperm cells of abnormal morphology is associated with the duration of exposure to the waves emitted by the GSM phone. It was also confirmed that a decrease in the percentage of sperm cells in vital progressing motility in the semen is correlated with the frequency of using mobile phones.

**Weisbrot D, Lin H, Ye L, Blank M, Goodman R. (2003) Effects of mobile phone radiation on reproduction and development in *Drosophila melanogaster*. *Journal of Cell Biochemistry* 89(1):48-55.**

In this report we examined the effects of a discontinuous radio frequency (RF) signal produced by a GSM multiband mobile phone (900/1,900 MHz; SAR approximately 1.4W/kg) on *Drosophila melanogaster*, during the 10-day developmental period from egg laying through pupation. As found earlier with low frequency exposures, the non-thermal radiation from the GSM mobile phone increased numbers of offspring, elevated hsp70 levels, increased serum response element (SRE) DNA-binding and induced the phosphorylation of the nuclear transcription factor, ELK-1. The rapid induction of hsp70 within minutes, by a non-thermal stress, together with identified components of signal transduction pathways, provide sensitive and reliable biomarkers that could serve as the basis for realistic mobile phone safety guidelines.

**Weyandt, TB, Schrader, SM, Turner, TW, Simon, SD. (1996) Semen analysis of military personnel associated with military duty assignments. *Reproductive Toxicology* 10(6):521-528.**

A collaborative study between the U.S. Army Biomedical Research and Development Laboratory (USABRDL) and the National Institute for Occupational Safety and Health (NIOSH) was designed to assess fecundity of male artillery soldiers with potential exposures to airborne lead aerosols. Potential exposure assessment was based upon information provided in an interactive questionnaire. It became apparent from extensive questionnaire data that many soldiers in the initial control population had potentially experienced microwave exposure as radar equipment operators. As a result, a third group of soldiers without potential for lead or microwave exposures, but with similar environmental conditions, was selected as a comparison population. Blood hormone levels and semen analyses were conducted on artillerymen (n = 30), radar equipment operators (n = 20), and the comparison group (n = 31). Analysis of the questionnaire information revealed that concern about fertility problems motivated participation of some soldiers with potential artillery or

microwave exposures. Although small study population size and the confounding variable of perceived infertility limit the reliability of the study, several statistically significant findings were identified. Artillerymen who perceived a possible fertility concern demonstrated lower sperm counts/ejaculate ( $P = 0.067$ ) and lower sperm/mL ( $P = 0.014$ ) than the comparison group. The group of men with potential microwave exposures demonstrated lower sperm counts/mL ( $P = 0.009$ ) and sperm/ejaculate ( $P = 0.027$ ) than the comparison group. Variables used to assess endocrine, accessory sex gland, and sperm cell function were not different than the comparison group. Additional studies, incorporating larger numbers of individuals, should be performed in order to more optimally characterize potential lead and microwave exposure effects on male fecundity.

**Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS (2007) Effects of cellular phone emissions on sperm motility in rats. *Fertility and Sterility* 88(4):957-64.**

**OBJECTIVE:** To evaluate the effects of cellular phone emissions on rat sperm cells.

DESIGN: Classic experimental.

SETTING: Animal research laboratory.

SUBJECTS: Sixteen 3-month-old male Sprague-Dawley rats, weighing 250-300 g.

INTERVENTION(S): Rats in the experimental group were exposed to two 3-hour periods of daily cellular phone emissions for 18 weeks; sperm samples were then collected for evaluation.

MAIN OUTCOME MEASURE(S): Evaluation of sperm motility, sperm cell morphology, total sperm cell number, and mRNA levels for two cell surface adhesion proteins.

RESULT(S): Rats exposed to 6 hours of daily cellular phone emissions for 18 weeks exhibited a significantly higher incidence of sperm cell death than control group rats through chi-squared analysis. In addition, abnormal clumping of sperm cells was present in rats exposed to cellular phone emissions and was not present in control group rats.

CONCLUSION(S): These results suggest that carrying cell phones near reproductive organs could negatively affect male fertility.

**Yoshida Y, Seto T, Ohsu W, Hayashi S, Okazawa T, Nagase H, Yoshida M, Nakamura H (1995) [Endocrine mechanism of placental circulatory disturbances induced by microwave in pregnant rats]. *Nippon Sanka Fujinka Gakkai Zasshi* 47(2):101-108. [Article in Japanese]**

Effects of microwaves on fetus and female genital organs remain to be elucidated. To demonstrate the placental circulatory disturbances induced by microwaves and to clarify the endocrine pathogenesis, placental blood flow and five endocrine indicators, i.e., corticosterone (CS), estradiol (E2), progesterone (P), prostaglandin E2 (PGE2) and prostaglandin F2 alpha (PGF2 alpha) were measured in rats exposed to whole-body microwaves with an intensity of 10 mW/cm<sup>2</sup> at a frequency of 2,450 MHz. The placental blood flow at 45-90 min after exposure was significantly decreased in the rats exposed to the microwaves. Placental blood flow at 15 and 30 min was increased by pretreatment with intraperitoneal administration of angiotensin II (AII). In contrast, no significant change in placental blood flow was recognized in the AII pretreated rats exposed to the microwaves. An increase in CS and a decrease in E2 were induced by the microwave exposure independent of pretreatment with AII. P was increased by microwave exposure in the rats without pretreatment with AII. PGE2 was not changed by the microwave exposure in the case of either nonpretreatment or pretreatment with AII. PGF2 alpha was increased by the microwave exposure in the rats without pretreatment with AII. The present results indicate that excessive exposure to whole-body microwave disorders pregnancy in terms of placental circulatory dysfunction. The data suggest the involvement of endocrine mechanisms in the decrease in placental blood flow which is



induced via a detrimental effect of microwaves on PGF2 alpha and on pituitary functions such as general emotional stress.

**Youbicier-Simo, BJ, Lebecq, JC, Bastide, M. (1998) Mortality of chicken embryos exposed to EMFs from mobile phones. Presented at the Twentieth Annual Meeting of the Bioelectromagnetics Society, St. Pete Beach, FL, June 1998. Exposure to mobile phone-radiated EMFs during development worsens embryonic mortality in chicken.**

Conclusion: Exposure to mobile phone-radiated EMFs during development worsens embryonic mortality in chickens.

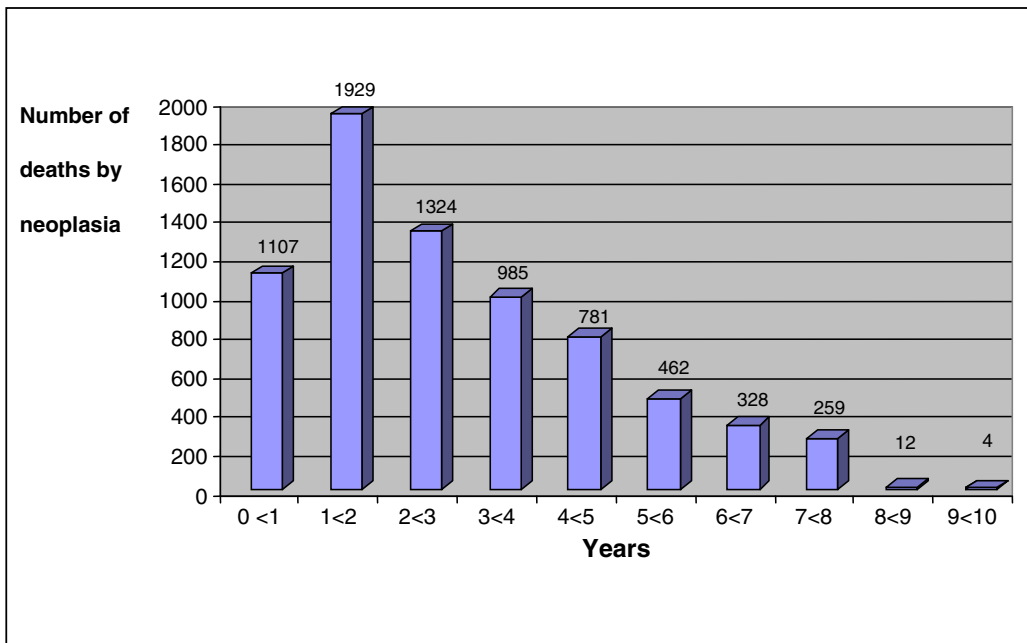
Method: We previously reported that continuous exposure of chicken embryos to electromagnetic fields (EMFs) emitted by television and computer worsens embryonic death (Bioelectromagnetics, 1997, 18: 514-523). The present study was designed to assess the effects of EMFs radiated by mobile phones on the development of chicken embryos. Two groups of 60 eggs each were incubated (21 days,  $38 \pm 1^\circ\text{C}$ , 45-55% humidity, permanent darkness) under the following electromagnetic exposure conditions: control group (without the telephone); exposed group (24h/24h exposure with the telephone switched on and placed downwards, 10 mm above the eggs; the letter were distributed on a plateform with locations numbered from 1 to 60; see exposure system in page 2). The mobile phone used (Bosch, CARTEL SL 2G2, Germany) radiates in the radiofrequency band with 2 W power. The VLF and ELF values measured at different positions at the level of the eggs are outlined as ratios, adjacent to the exposure system (page 2). The values over and under the bar correspond to the telephone switched off and on respectively. Embryonic mortality was evaluated by candling the eggs and numbering dead embryos at two-day intervals from embryonic day 3 (ED3) to embryonic day 13 (ED13): ED3, ED5, ED7, ED9, ED11, ED13. Counting could not be performed from ED14 to hatching (ED21) because the eggs had become so opaque (intense vascularization, increased embryo body size) that the embryos could hardly be mirrored through the shell. For the latter period, embryonic mortality was assessed by opening the eggs from which the chicks did not hatch at ED21. Three independent experiments were carried out. Embryonic mortality was expressed either as cumulative mortality (previous + current counts) or as total death rate (percentage of necropsied embryos from ED3 to ED21). In the exposed group, EMF exposure was accompanied by increased embryonic loss during the whole embryonic period, while noticeable variations in the control group occurred mainly at the end of incubation (ED21); furthermore mean total death rate (TDR) for the three experiments was 6-fold higher in EMF-exposed group than in their control counterparts (72.3% vs. 11.9%; see Table 1). Consistently, necropsy distribution in the exposed group was essentially restricted to an area around the source of EMF (mobile phone), which contrast with rather sparse distribution in the control group (see the diagrams of cumulative mortality in page 2). Together these findings demonstrate that exposure to mobile phones-radiated EMFs during development worsens embryonic mortality. [Note that this experiment was funded by the company which made the protection-antenna being tested. SF.]

<http://www.electric-words.com/cell/abstracts/yo13240.html>

**Note: For seven or more, the names and initials of the first three should be given, followed by et al. All names appear here for future work and then repeated the first three et al. for this journal.**

Fertility; Effects of Microwave RF Exposure on  
Fertility, Dr. Paul Dart MD. (Petitioner); 2013

## Belo Horizonte, Brazil (2011)



Death rates peaked during the second year of exposure.

Fig. 16. Distribution of the number of deaths by neoplasia versus duration of exposure since the date that the first antenna in each analyzed CT came into operation.

Dode AC, Leao MM, Tejo Fde A et al. Mortality by neoplasia and cellular telephone base stations in the Belo Horizonte municipality, Minas Gerais state, Brazil. *Sci Total Environ* (2011); 409(19):3649-3665.

## Effects of Microwave RF Exposure on Fertility



## Impaired Fertility in Fruit Flies



Insects are remarkably resistant to ionizing radiation and radioactivity.

They appear to be much more sensitive to the effects of microwave radio frequency exposures.

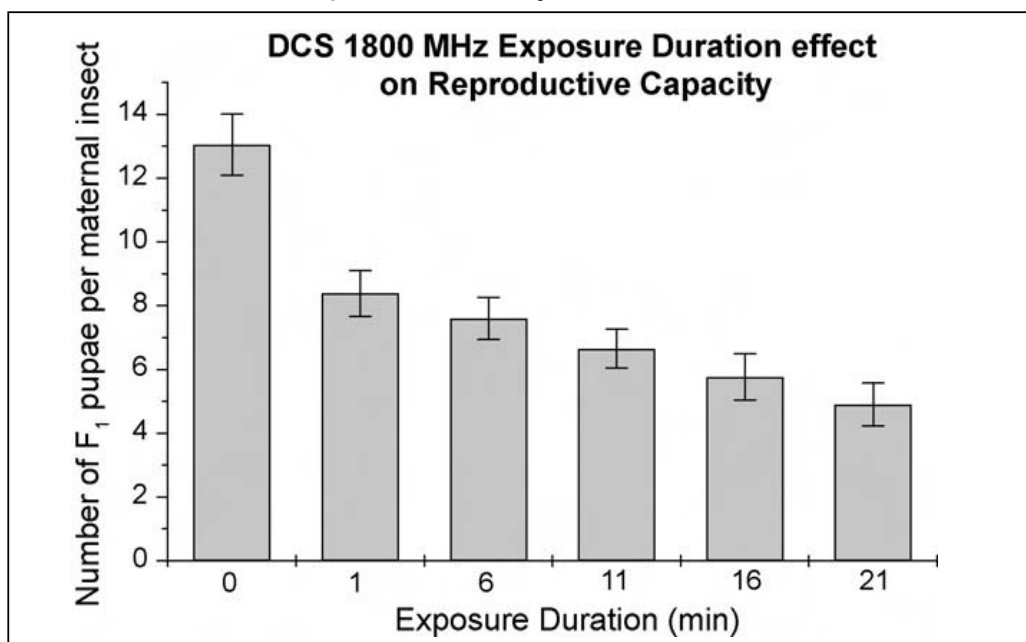
In a recent study, **fruit flies were exposed to 10  $\mu\text{W}/\text{cm}^2$  of GSM 900 MHz or 1800 MHz digital RF.**

**This exposure level is 100 times lower than the FCC Guidelines of 1000  $\mu\text{W}/\text{cm}^2$**

Exposures were for one single exposure intervals per day for five days, ranging from 1 to 21 minutes per day.

Panagopoulos DJ, Margaritis LH. The effect of exposure duration on the biological activity of mobile telephony radiation. *Mutat Res* (2010); 699(1-2):17-22.

## Impaired Fertility in Fruit Flies



0 = control group, with no exposure.

**Even at one minute of exposure per day, a significant decrease in fertility is seen.**

Fig. 2. Reproductive capacity (mean number of F1 pupae per maternal fly) of groups exposed to DCS 1800MHz radiation for different daily exposure durations (1, 6, 11, 16, and 21min) for five consecutive days, and of sham-exposed groups (no exposure).

Panagopoulos DJ, Margaritis LH. The effect of exposure duration on the biological activity of mobile telephony radiation. *Mutat Res* (2010); 699(1-2):17-22.

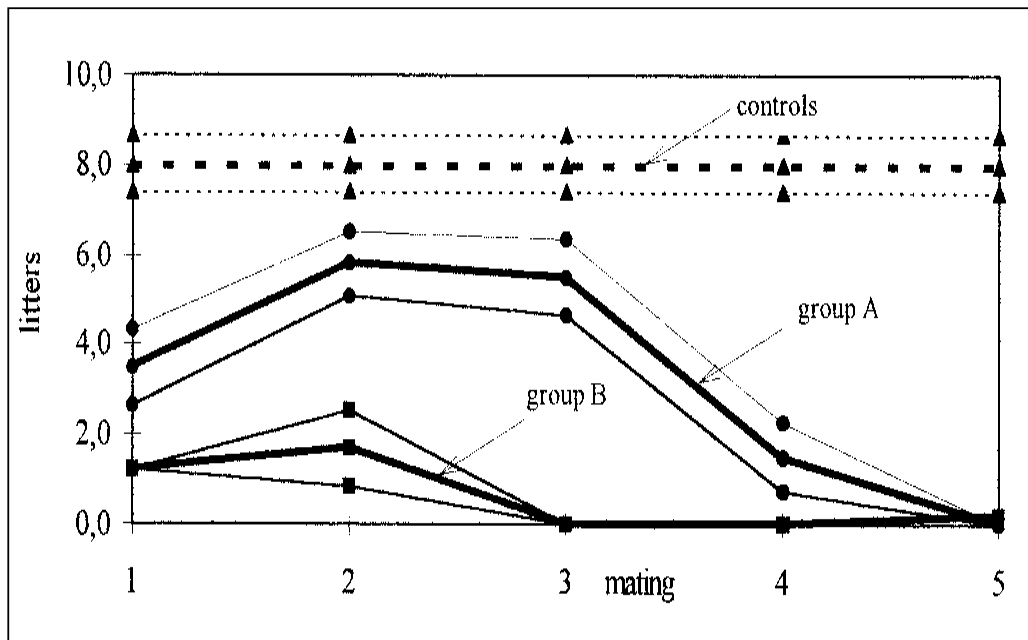
## Impaired Fertility in Mammals



This is a Wistar rat.

A great deal of research has been done on the effects of microwave RF on laboratory animals.

## Impaired Fertility in Female Mice



In one study, mice were kept in cages in a VHF/UHF antenna park in Thessaloniki, Greece.

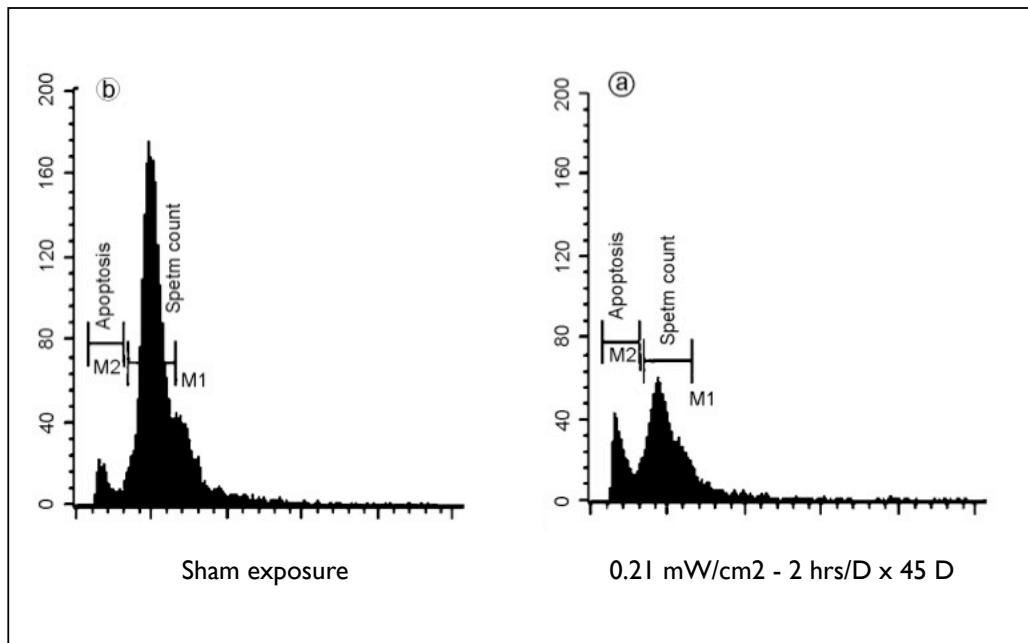
Power densities ranged between  $0.168$  to  $1.053 \mu\text{W}/\text{cm}^2$  [reported as 168 – 1053 nanowatts/ $\text{cm}^2$ ]

**This is about 1000 times lower than the FCC Guidelines of  $600\text{--}1000 \mu\text{W}/\text{cm}^2$**

With repeated matings, litter size decreased, until by the 5th mating, all the dams were infertile.

**This infertility was irreversible.**

## Impaired Fertility in Male Rats



Reduced sperm production in male Wistar rats exposed to 10 GHz microwave RF.

0.21 mW/cm<sup>2</sup> = **one fifth of the FCC Guidelines of 1 mW/cm<sup>2</sup>**

OTHER EFFECTS: Increases in reactive oxygen species, increased free radical formation, decreased activity of glutathione peroxidase and superoxide dismutase, DNA strand breakage, increased apoptosis (cell death) in sperm cells, distortion of sperm structure, reduced testosterone levels, shrinkage of seminiferous tubules and testicular size, decreased number and weight of progeny.

Kesari KK, Kumar S, Behari J. Effects of radiofrequency electromagnetic wave exposure from cellular phones on the reproductive pattern in male Wistar rats.

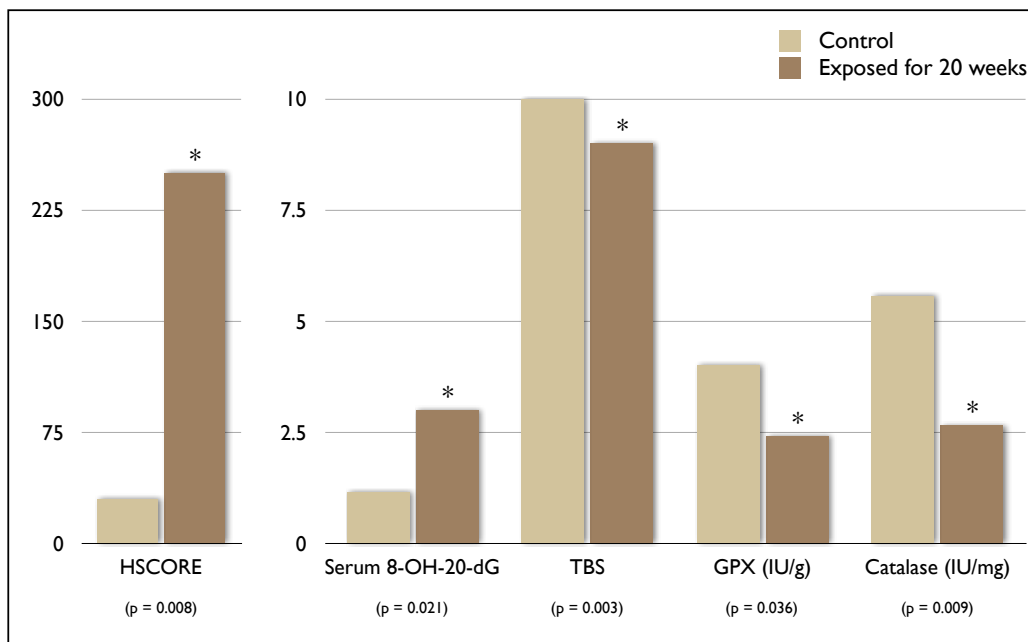
*Appl Biochem Biotechnol* (2011); 164(4):546-559.

Kesari KK, Kumar S, Behari J. Pathophysiology of microwave radiation: effect on rat brain. *Appl Biochem Biotechnol* (2012); 166(2):379-388.

Kumar S, Kesari KK, Behari J. Influence of microwave exposure on fertility of male rats. *Fertil Steril* (2011); 95(4):1500-1502.

Kumar S, Behari J, Sisodia R. Influence of electromagnetic fields on reproductive system of male rats. *Int J Radiat Biol* (2012); epub Nov 13:1-8

## WiFi Exposure Damages Sperm With Oxidant Stress.



The rats were exposed to a Standard WiFi gateway, 24 hours a day for 20 days.

**HSCORE** = histological staining in testes for 8-OH-20-dG  
[8-hydroxy-20-deoxyguanosine, **byproduct of DNA damage**]

**Serum 8-OH-20-dG** (ng/ml) [byproduct of DNA damage]

**TBS** = testicular biopsy score

9 = Much spermatogenesis, but germinal epithelium disorganized with marked sloughing or obliteration of lumen

**GPX** = glutathione peroxidase, an antioxidant (consumed by oxidative stress in exposed rats).

Atasoy HI, Gunal MY, Atasoy P, Elgun S, Bugdayci G. Immunohistopathologic demonstration of deleterious effects on growing rat testes of radiofrequency waves emitted from conventional Wi-Fi devices. *J Pediatr Urol* (2012); March 30.



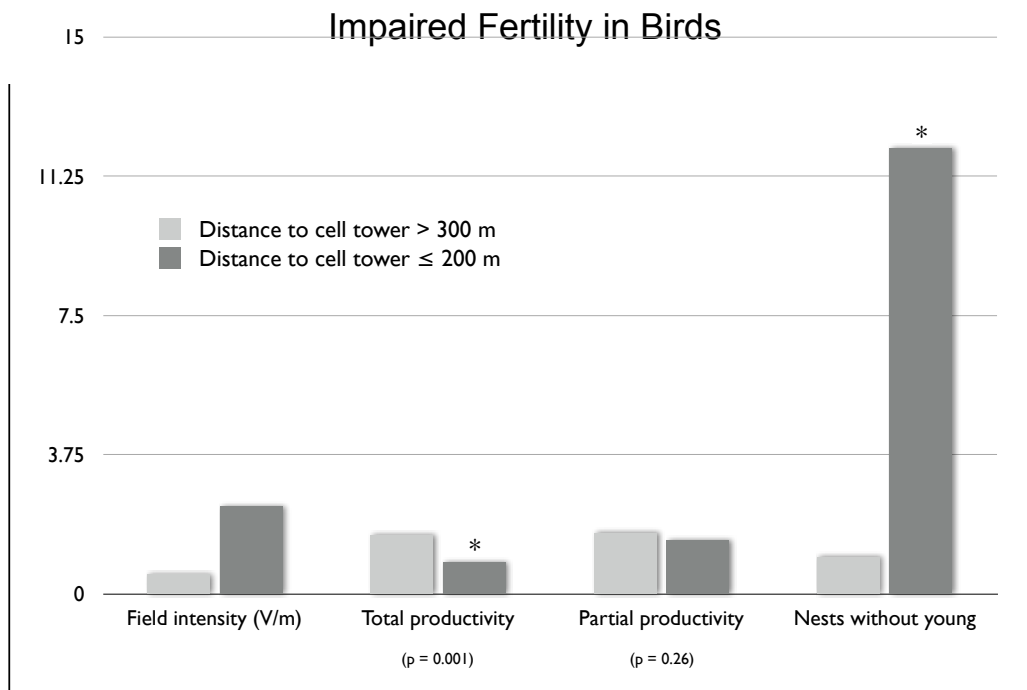
## Impaired Fertility in Birds



In Valladolid, Spain, a study compared the productivity of storks nesting closer and farther from a cell phone tower site.

30 nests within 200 meters of the antennae, were compared with 30 nests greater than 300 meters from the antennae

Balmori A. Possible Effects of Electromagnetic Fields from Phone Masts on a Population of White Stork. *Electromagn Biol Med* (2005); 24(2):109-119.



Productivity was significantly reduced in birds in the high exposure group.

Average electric field intensity on nests within 200m =  $2.36 \pm 0.82 \text{ V/m}$  (~  $1.48 \mu\text{W/cm}^2$ )

**This is more than 400 times less than the FCC Guidelines of 600–1000  $\mu\text{W/cm}^2$**

Average electric field intensity on nests further than 300m =  $0.53 \pm 0.82 \text{ V/m}$  (~  $0.07 \mu\text{W/cm}^2$ ).

Balmori A. Possible Effects of Electromagnetic Fields from Phone Masts on a Population of White Stork. *Electromagn Biol Med* (2005); 24(2):109-119.

## Impaired Fertility in Amphibians



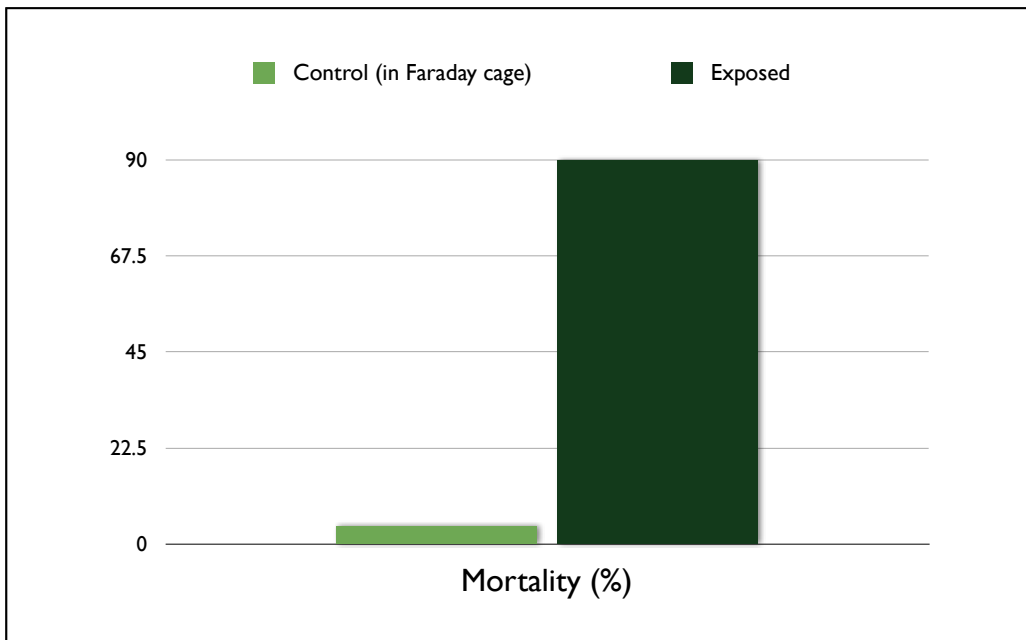
Eggs and tadpoles of the European common frog (*Rana temporaria*) were exposed to RF/EFM from several cell towers located at a distance of 140 meters.

**Duration of exposure was 2 months** (from egg phase to advanced tadpole stage).

Control groups were placed in same conditions, but contained in a faraday cage that shielded the eggs from RF exposure.

Balmori A. Mobile phone mast effects on common frog (*Rana temporaria*) tadpoles: the city turned into a laboratory. *Electromagn Biol Med* (2010a); 29(1-2):31-35.

## Impaired Fertility in Amphibians



Exposure intensity 1.8 to 3.5 V/m (~ 0.8–3.2  $\mu\text{W}/\text{cm}^2$ ).

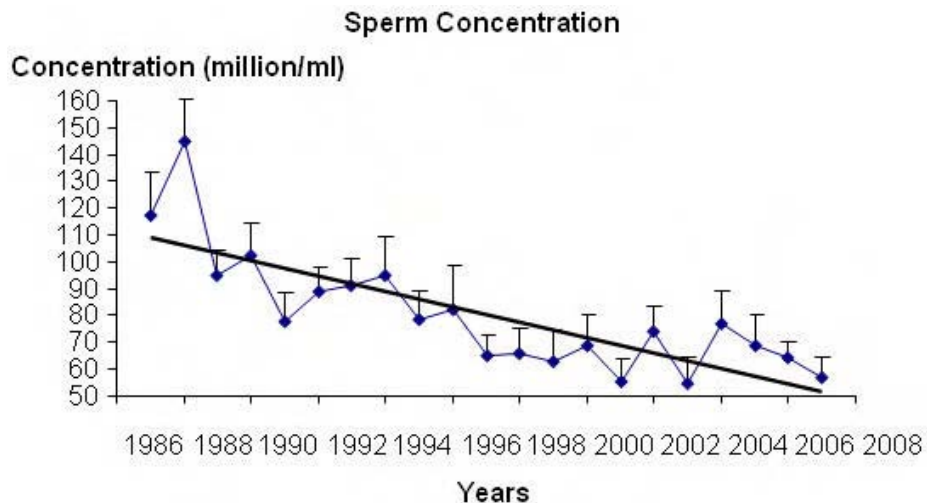
**This is 200 times less than the FCC Guidelines of 600–1000  $\mu\text{W}/\text{cm}^2$**

[In the exposed group (n = 70), low coordination of movements and asynchronous growth was observed in living specimens, resulting in both big and small tadpoles. In the control group (n = 70), growth was normal.]

Balmori A. Mobile phone mast effects on common frog (*Rana temporaria*) tadpoles: the city turned into a laboratory. *Electromagn Biol Med* (2010a); 29(1-2):31-35.

## Impaired Fertility in Humans

**Figure 2. Sperm concentration in 975 sperm donors recruited over 20 years**



Sperm counts have been dropping worldwide for the last several decades.

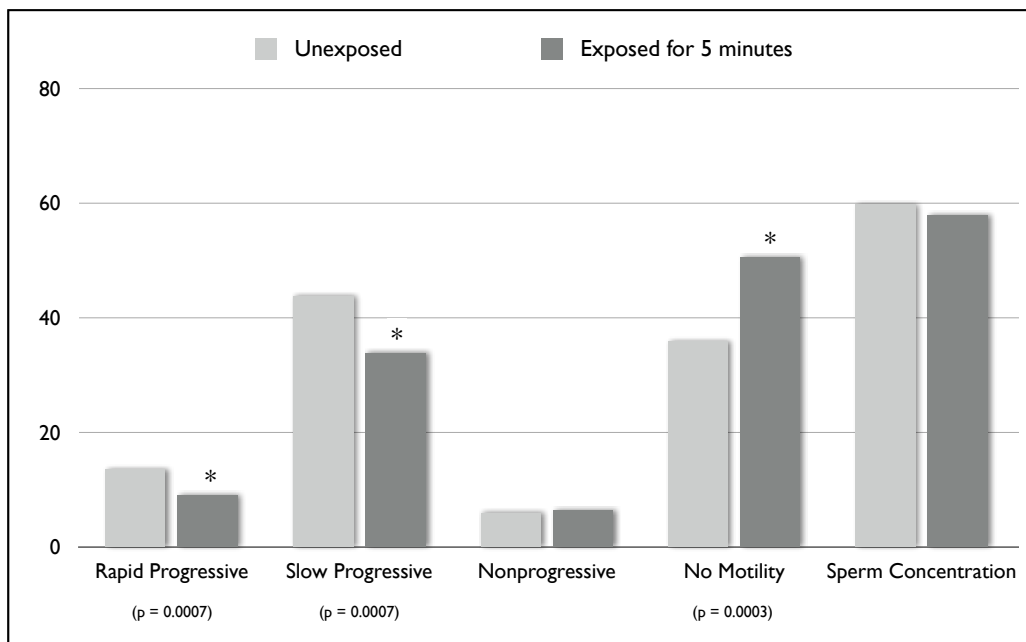
(e.g. In New Zealand, 2.5% per year for the last 20 years).

Pesticides have been implicated.

**Some evidence suggests that microwave RF exposure may also play a role.**

Shine R, Peek J, Birdsall M. Declining sperm quality in New Zealand over 20 years. *N Z Med J* (2008); 121(1287):50-56.

## Cell Phone Transmissions Decrease Sperm Motility in Vitro



Samples of human sperm received 5 minutes exposure, 10 cm from a transmitting GSM 900 MHz cell phone.

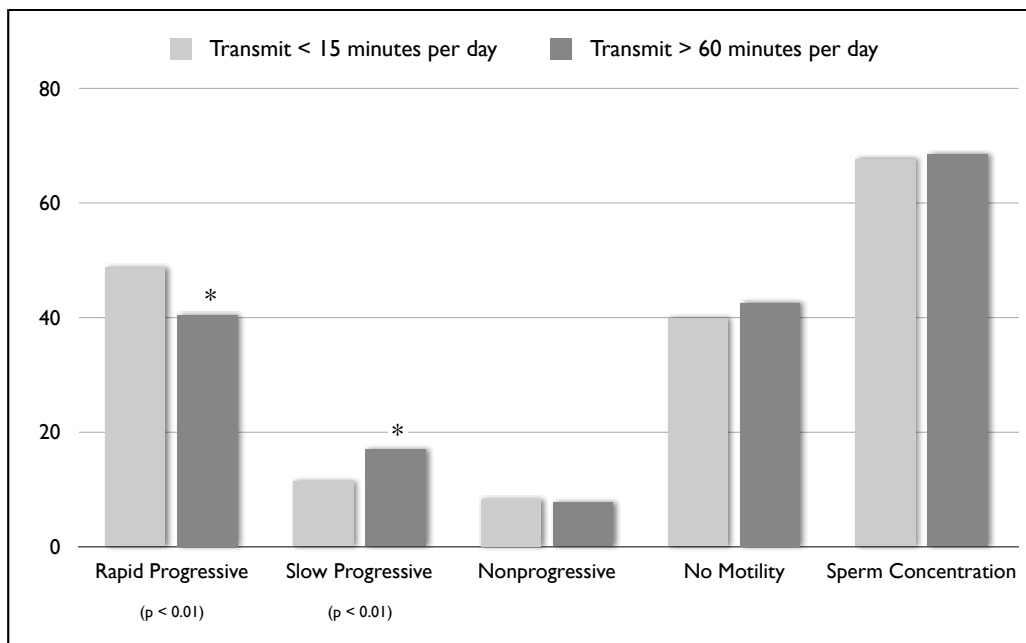
Average power density of exposure: 20  $\mu\text{W}/\text{cm}^2$

**This is 30 times less than the FCC Exposure Guideline of 600  $\mu\text{W}/\text{cm}^2$**

(Y axis = values in %)

Eroglu O, Oztas E, Yildirim I et al. Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study. *Arch Med Res* (2006); 37(7):840-843.

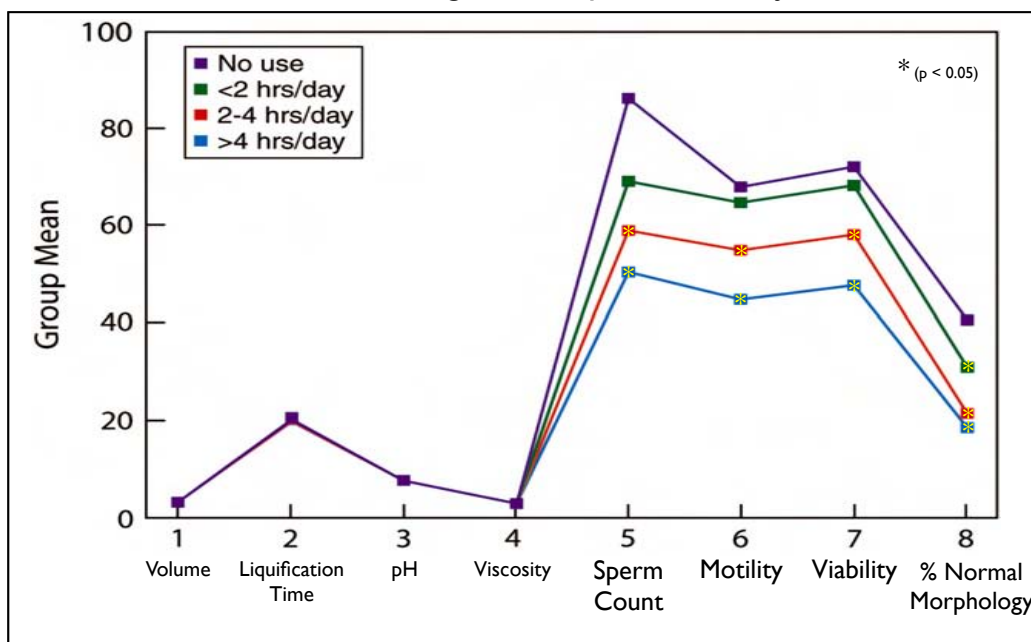
## Cell Phone Use Decreases Sperm Motility in Vivo



Semen analysis performed on 371 men at a university clinic.  
Health questionnaire included query of cell phone use habits.  
(Y axis = values in %)

Fejes I, Zavaczki Z, Szollosi J et al. Is there a relationship between cell phone use and semen quality? *Arch Androl* (2005); 51(5):385-393.

## Cell Phone Use Degrades Sperm Quality in Vivo



Three hundred sixty-one men undergoing infertility evaluation were divided into four groups according to their active cell phone use:

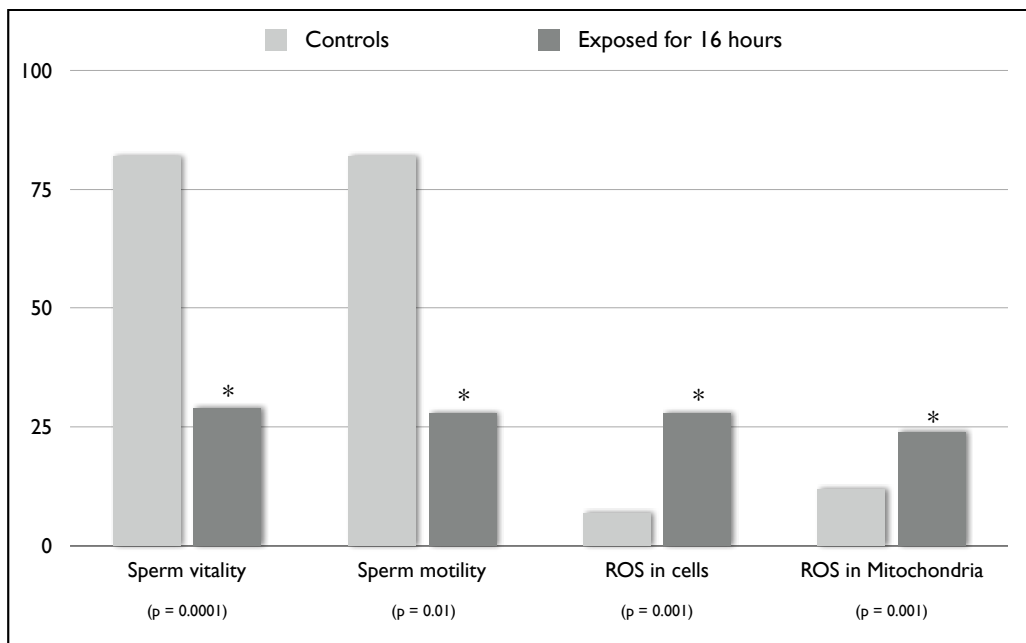
group A: no use; group B: <2 h/day; group C: 2-4 h/day; and group D: >4 h/day.

With greater than two hours a day of reported talk time, significant reduction in **sperm count, motility, viability, and % normal morphology** were observed.

[One can assume that with texting rather than talking, the data might be even worse . . . as the phone antenna will be closer to the testes.]

Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. *Fertil Steril* (2008); 89(1):124-128.

## Isothermal Exposure to 1.8 GHz RF Damages Sperm



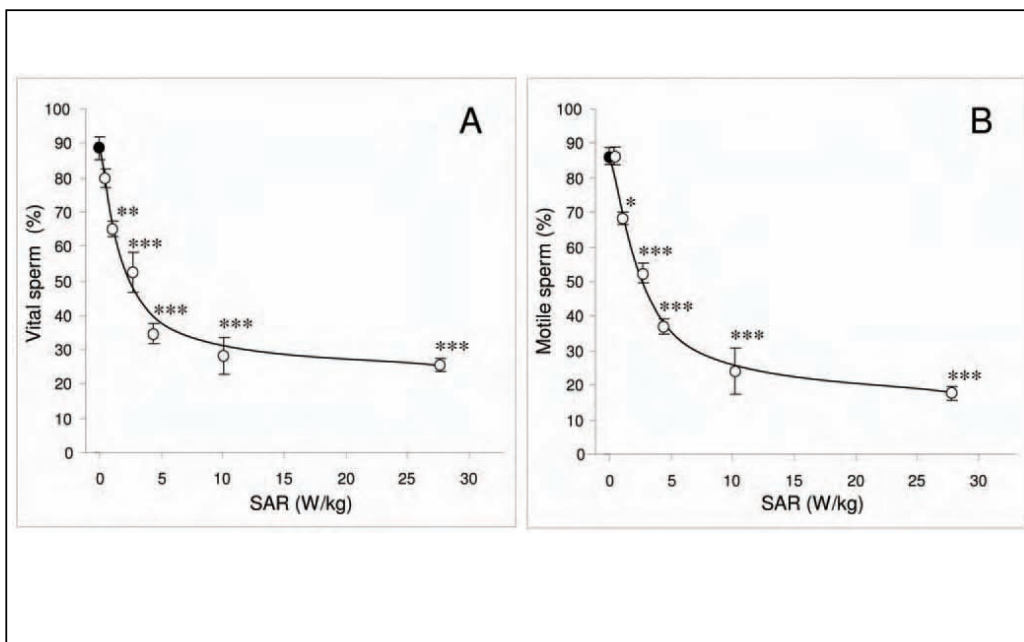
**Sperm exposed for 16 hours in vitro to 1.8 GHz (SAR = 27.5 W/kg) @ 21°C (isothermal conditions).**

Sperm damage correlates with increased free radical (ROS) production.

Values in %.

De Iuliis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. *PLoS One* (2009); 4(7):e6446 (1-9).

## 1.8 GHz RF Degrades Sperm Quality In Vitro



1.8 GHz RF at various intensities for 16 hours @ 21°C

This is an isothermal exposure

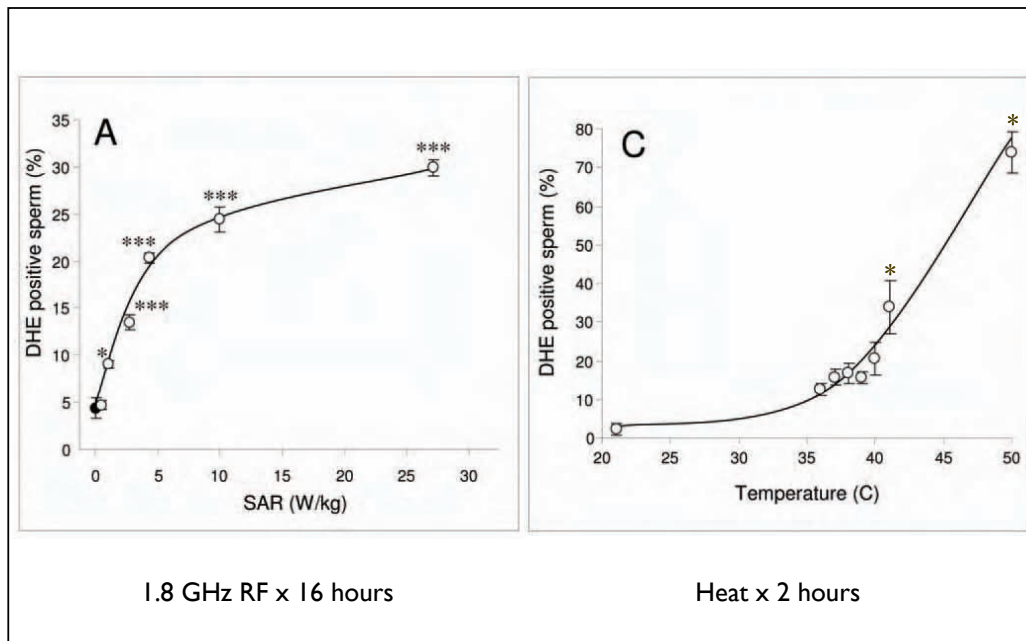
Sperm vitality and motility are significantly detracted at SAR = 1 W/kg and above

Figure 2. RF-EMR exposure reduces motility and vitality of human spermatozoa, in an SAR dependent manner. Percoll-purified spermatozoa ( $5 \times 10^6$  cells) were suspended in 1 ml BWB in a 35 mm Petri dish and placed within the waveguide while control cells (closed circles) were placed outside the waveguide. Cells in the waveguide were exposed to 1.8 GHz RF-EMR at SAR levels of 0.4, 1.0 2.8 4.3 10.1 and 27.5 W/kg (open circles) for 16 h at 21°C. Both vitality and motility were reduced in a dose dependent manner.

A, Vitality was significantly reduced at a SAR of 1.0 W/kg from  $89\% \pm 3\%$  to  $65\% \pm 1\%$  (\*\*p.0.01).

B, Motility was also significantly reduced at a SAR of 1.0 W/kg from  $86\% \pm 2\%$  to  $68\% \pm 2\%$  (\*p.0.05). All results are based on 4 independent samples.

## ROS Production – RF versus Thermal



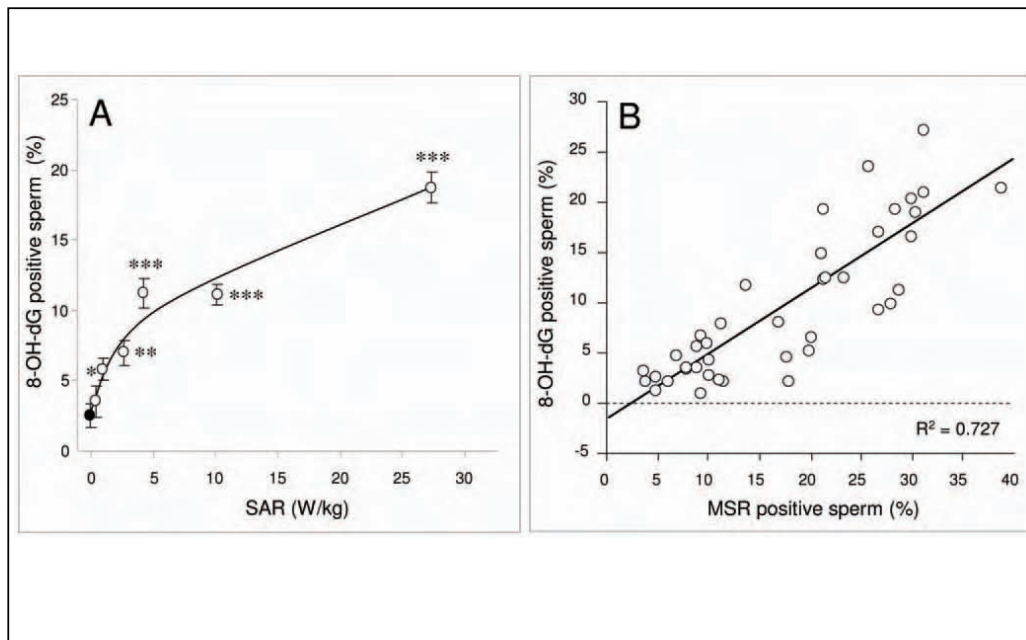
A. ROS generation (DHE response) was significantly increased from control levels after exposure to 1.0 W/kg (\*p, 0.05) and above (\*\*\*p, 0.001).

C. In order to control for thermal effects, the impact of temperature of cellular ROS generation was monitored; a significant increase in ROS generation was observed as temperatures rose above 40°C (p, 0.001).

Figure 3. RF-EMR induces ROS generation in human spermatozoa, in an SAR-dependent manner unrelated to thermal effects.

De Iuliis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. *PLoS One* (2009); 4(7):e6446 (1-9).

## Oxidative Damage To Sperm DNA From 1.8 GHz RF Exposure



1.8 GHz RF x 16 hours @ 21°C isothermal.

A) As the power levels were increased, the amount of oxidative DNA damage expressed also increased.

A significant amount of oxidative DNA damage was observed in cells exposed to 2.8 W/kg (\*p, 0.05) RF-EMR and above (\*\*p, 0.01; \*\*\*p, 0.001).

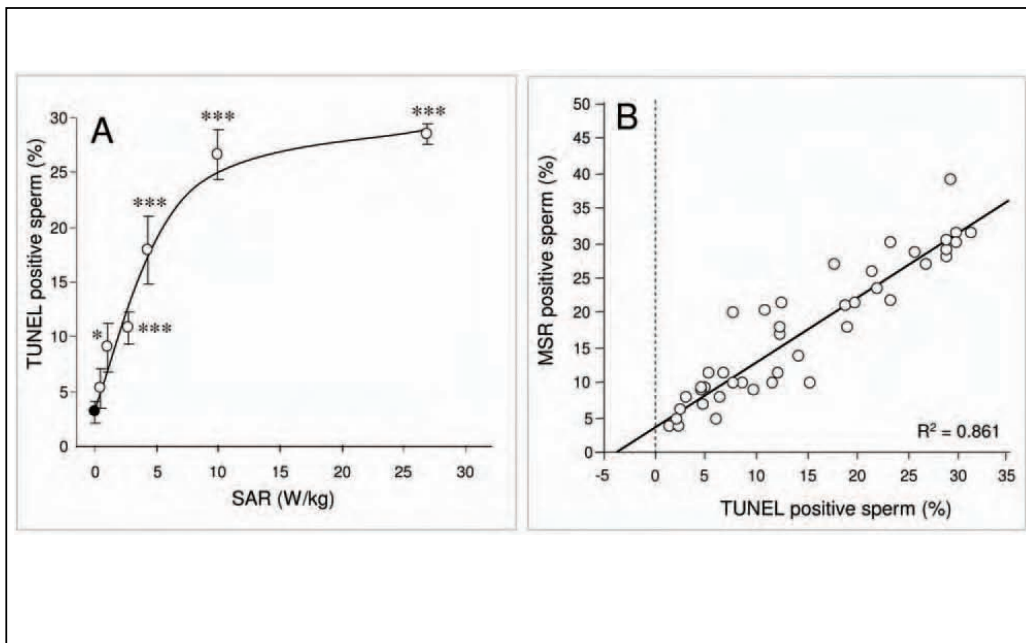
B) The levels of 8-OH-dG expression were positively correlated with the levels of ROS generation by the mitochondria ( $R^2 = 0.727$ ).

Figure 4. RF-EMR induces oxidative DNA damage in human spermatozoa.

De Iuliis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. *PLoS One* (2009); 4(7):e6446 (1-9).



## RF Damages Sperm by Increasing Oxidative Stress



A) Significant levels of DNA fragmentation was observed in exposed spermatozoa at 2.8 W/kg (\*p,0.05) and above (\*\*p,0.001).

B) DNA fragmentation was positively correlated with ROS production by the mitochondria as monitored by MSR. ( $R^2 = 0.861$ ).

Figure 5. RF-EMR induces DNA fragmentation in human spermatozoa.

De Iuliis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. *PLoS One* (2009); 4(7):e6446 (1-9).



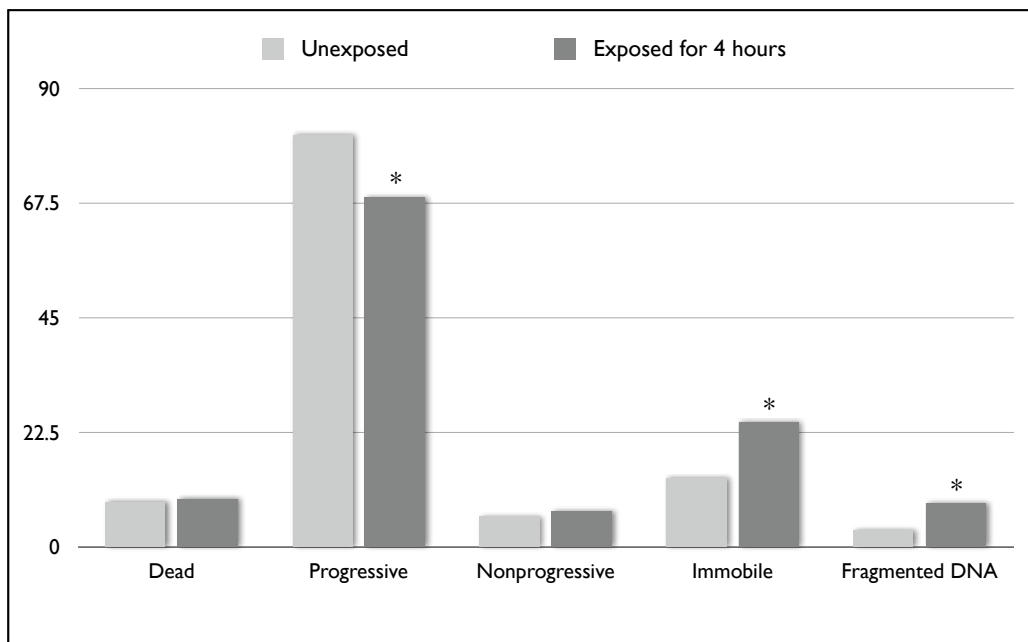


Motile spermatozoa in semen were incubated at room temperature,  
3 cm below laptop computer (e.g. lap distance)  
4 hours of exposure.

Control incubated in similar conditions, without presence of the computer.

Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. *Fertil Steril* (2012); 97(1):39-45.

## Sperm Damage From Laptop WiFi



Power density ranged 0.45 to 1.05  $\mu\text{W}/\text{cm}^2$

[This is roughly **1000 times less** than the FCC exposure limit of 1000  $\mu\text{W}/\text{cm}^2$ ]

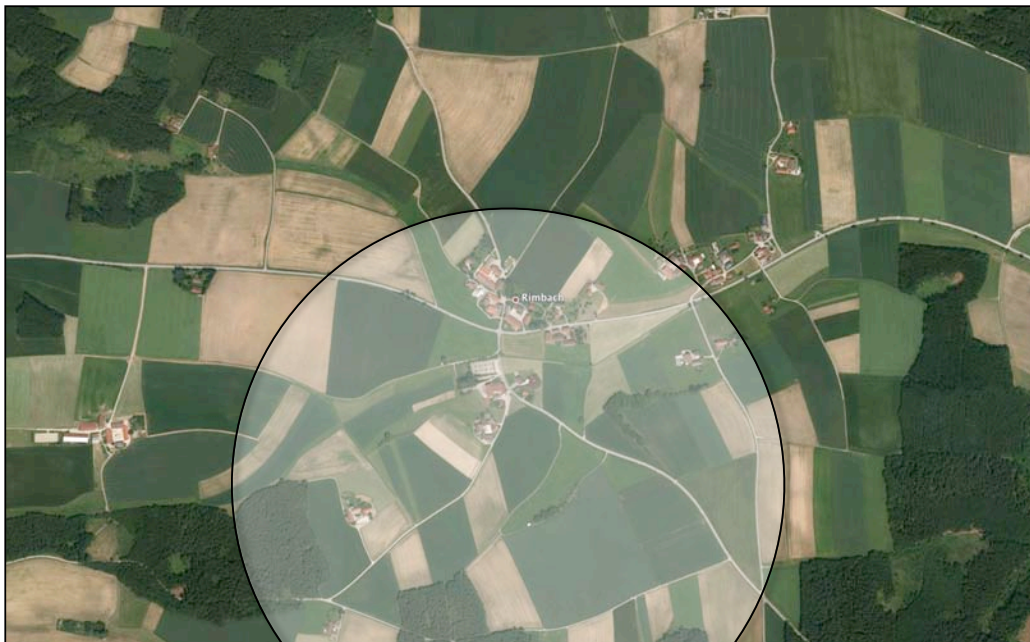
Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. *Fertil Steril* (2012); 97(1):39-45.

Hormonal; RF and Hormones, Alterations in Hormone  
Physiology; Dr. Paul Dart MD. (Petitioner); 2013

# Alterations in Hormone Physiology



## Rimbach, Bavaria (2004 - 2005)



In spring of 2004 a GSM cell tower was installed near Rimbach, Bavaria (population ~ 2000).

Prior to activation of the antenna, the town residents were asked to participate in a mass screening.

Urine levels of the stress hormones adrenaline, noradrenaline, dopamine, and phenylethylamine were measured in January/February 2004, and again in July 2004, January 2005, and July 2005.

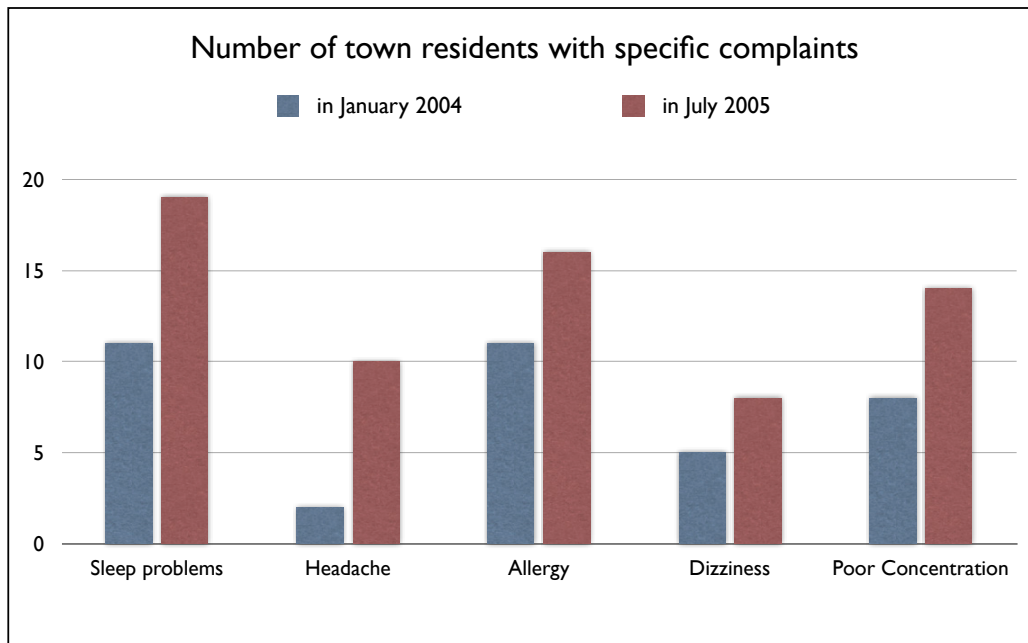
A medical history and symptom questionnaire was also administered.

-

-----  
Buchner K EH. Changes of Clinically Important Neurotransmitters under the Influence of Modulated RF Fields--A Long-term Study under Real-life Conditions. *Umwelt-Medizin-Gesellschaft* (2011); 24(1):44-57.

JA 05501

## Rimbach, Bavaria (2004 - 2005)

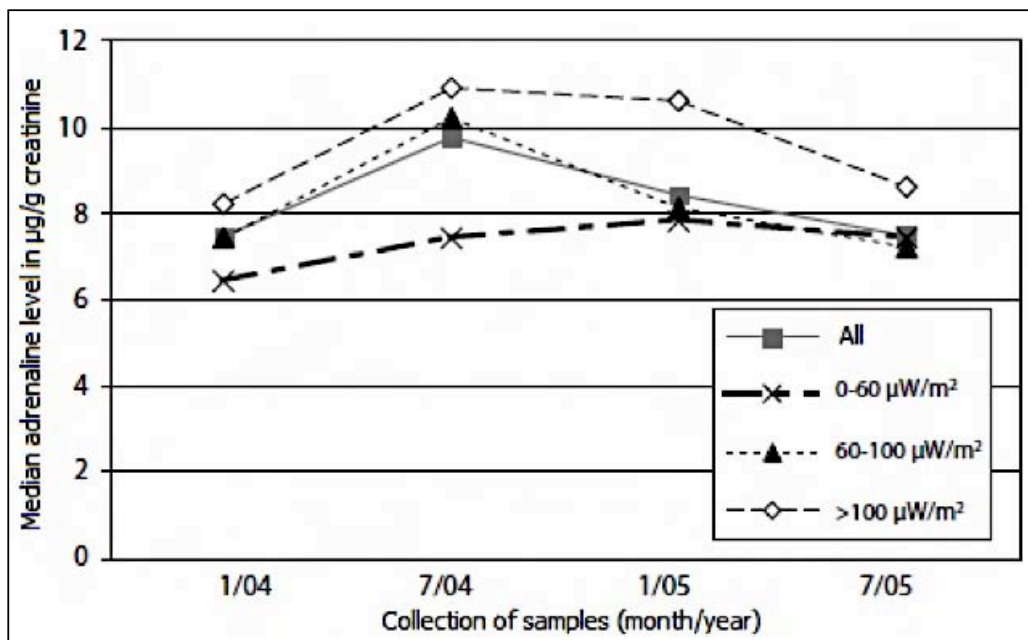


Here we see some symptom scores before tower activation (blue) and after a year of tower transmission (red)  
Some health complaints increased over the course of the study.

Buchner K EH. Changes of Clinically Important Neurotransmitters under the Influence of Modulated RF Fields--A Long-term Study under Real-life Conditions. *Umwelt-Medizin-Gesellschaft* (2011); 24(1):44-57.

Abstract: This follow-up of 60 participants over one and a half years shows a significant effect on the adrenergic system after the installation of a new cell phone base station in the village of Rimbach (Bavaria). After the activation of the GSM base station, the levels of the stress hormones adrenaline and noradrenaline increased significantly during the first six months; the levels of the precursor dopamine decreased substantially. The initial levels were not restored even after one and a half years. As an indicator of the dysregulated chronic imbalance of the stress system, the phenylethylamine (PEA) levels dropped significantly until the end of the study period. The effects showed a dose-response relationship and occurred well below current limits for technical RF radiation exposures. Chronic dysregulation of the catecholamine system has great relevance for health and is well known to damage human health in the long run.

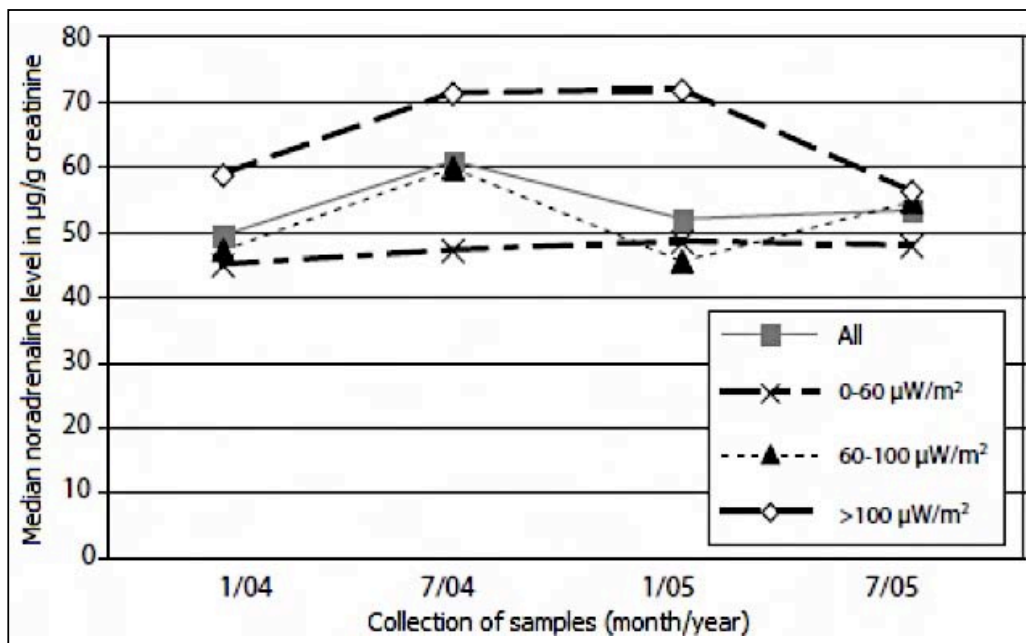
## Adrenaline levels



Results were stratified by in-home exposure levels ( $\text{mW}/\text{m}^2$ ) in three cohorts.  
Hormone levels graphed for each exposure cohort.  
Levels of the stress hormone adrenaline rose after the transmitter became active.  
In the highest exposure cohort adrenaline levels never returned to pre-exposure baseline.

Fig. 3: Median adrenaline levels for all participating citizens of Rimbach whose cell phone base station exposure was above  $100 \mu\text{W}/\text{m}^2$ , between 60 and  $100 \mu\text{W}/\text{m}^2$ , or up to  $60 \mu\text{W}/\text{m}^2$ . The power density levels refer to peak values of the GSM radiation exposure in front of a given residence.

## Noradrenaline levels



Noradrenaline levels also rose after the transmitter became active.

They never returned to pre-exposure baseline.

Fig. 7: Median noradrenaline levels in all participating citizens of Rimbach as a function of GSM power density levels (peak values)

## Effect of cordless DECT phones.

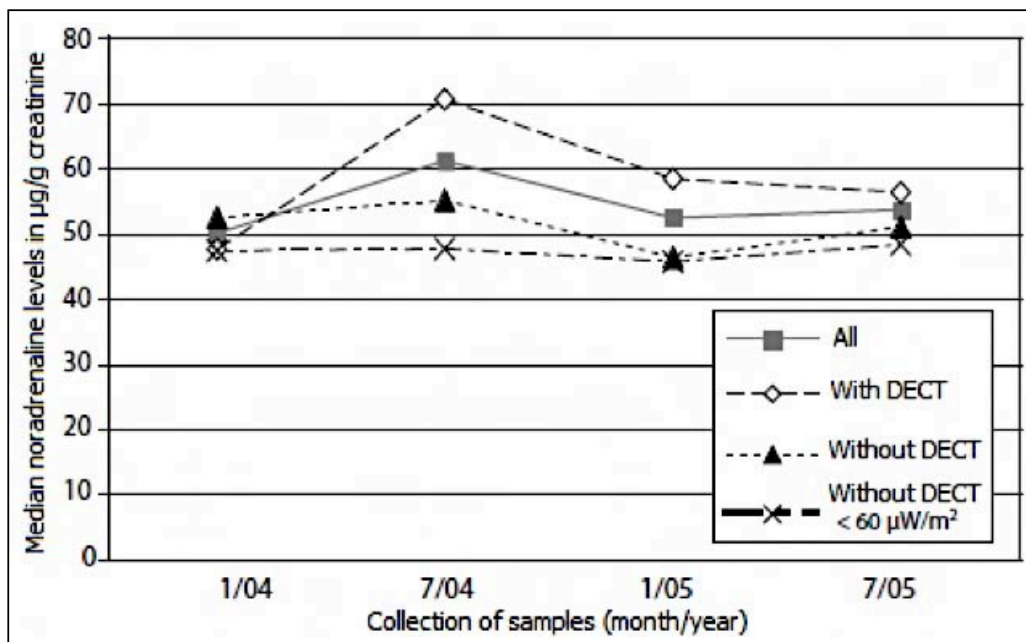
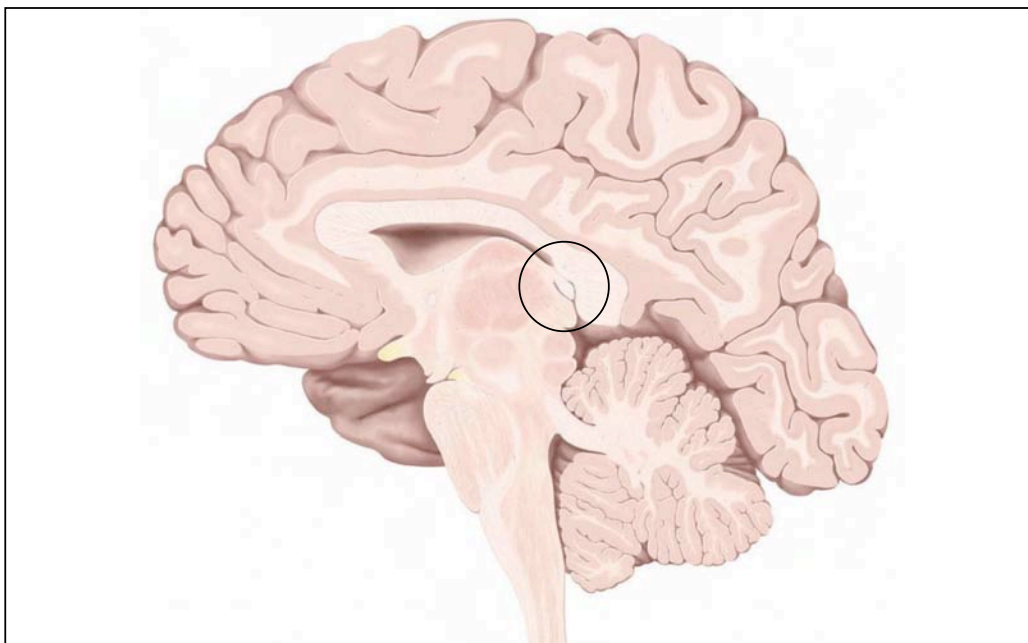


Fig. 8: Median noradrenaline values for subjects who had a DECT phone or other wireless devices at home, for those without indoor wireless devices, as well as for subjects without indoor wireless devices and with a GSM radiation exposure up to 60 µW/m<sup>2</sup> (peak value measured in front of residence)

Buchner K EH. Changes of Clinically Important Neurotransmitters under the Influence of Modulated RF Fields--A Long-term Study under Real-life Conditions. Umwelt-Medizin-Gesellschaft (2011); 24(1):44-57.

Abstract: This follow-up of 60 participants over one and a half years shows a significant effect on the adrenergic system after the installation of a new cell phone base station in the village of Rimbach (Bavaria). After the activation of the GSM base station, the levels of the stress hormones adrenaline and noradrenaline increased significantly during the first six months; the levels of the precursor dopamine decreased substantially. The initial levels were not restored even after one and a half years. As an indicator of the dysregulated chronic imbalance of the stress system, the phenylethylamine (PEA) levels dropped significantly until the end of the study period. The effects showed a dose-response relationship and occurred well below current limits for technical RF radiation exposures. Chronic dysregulation of the catecholamine system has great relevance for health and is well known to damage human health in the long run.

## Melatonin

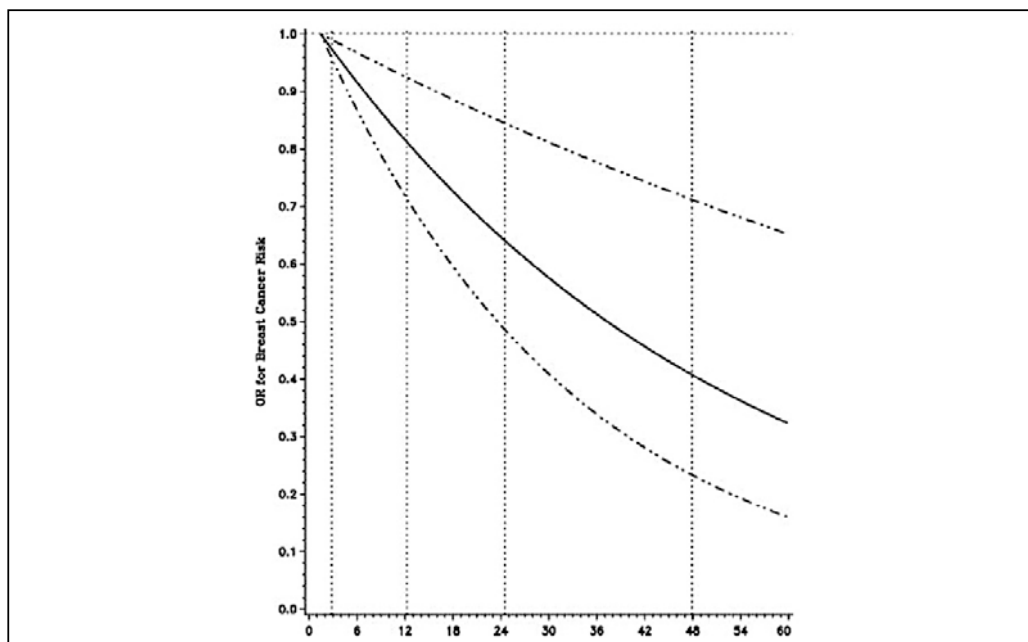


The pineal gland secretes melatonin. Ambient light suppresses melatonin secretion. So melatonin secretion is high during the night-time hours, peaking shortly after midnight. **Higher melatonin levels are part of what makes us feel “sleepy” at night.**

**Exposure to light during the night-time hours will lead to a rapid suppression of melatonin secretion by the pineal gland,** and this can cause disruption of sleep and derangement of the circadian rhythm.

Melatonin is one of the most potent anti-oxidant molecules in the human body, and acts to reduce reactive oxidative processes in the body. Melatonin can quench the damaging free radical activity produced by inflammation. The presence of elevated melatonin at night is therefore a key factor in the healing and rejuvenating functions that we associate with “a good night’s sleep”.

## Melatonin lowers risk of breast cancer.



[Figure 1. Smoothing spline plot for aMT6s level (ng/mg creatinine) in relation to breast cancer risk among postmenopausal women. 95% CIs are indicated by dotted lines.]

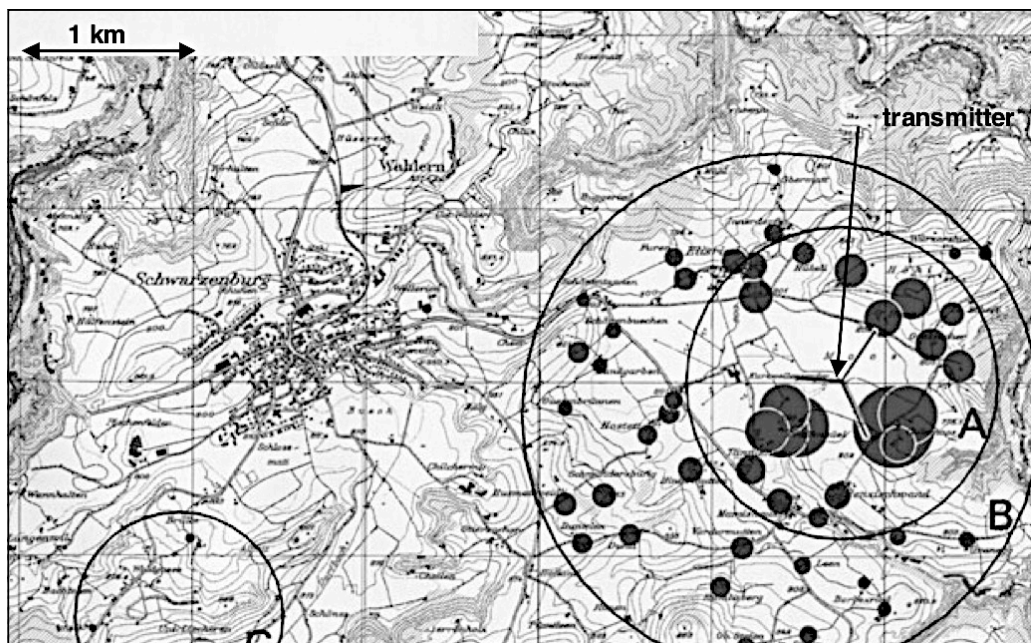
Melatonin is also protective against the growth of cancer cells, and disruption of the circadian melatonin cycle has been shown to lead to increased tumor growth in a variety of cancer types.

**Women who have lower levels of nocturnal melatonin are at greater risk for developing breast cancer.**

In 2007 the International Agency for Research on Cancer declared night shift work to be a probable carcinogen due to increased breast cancer risk..



## Schwarzenburg Short Wave Radio Broadcast Tower – 1998



RF exposure can also lower melatonin levels.

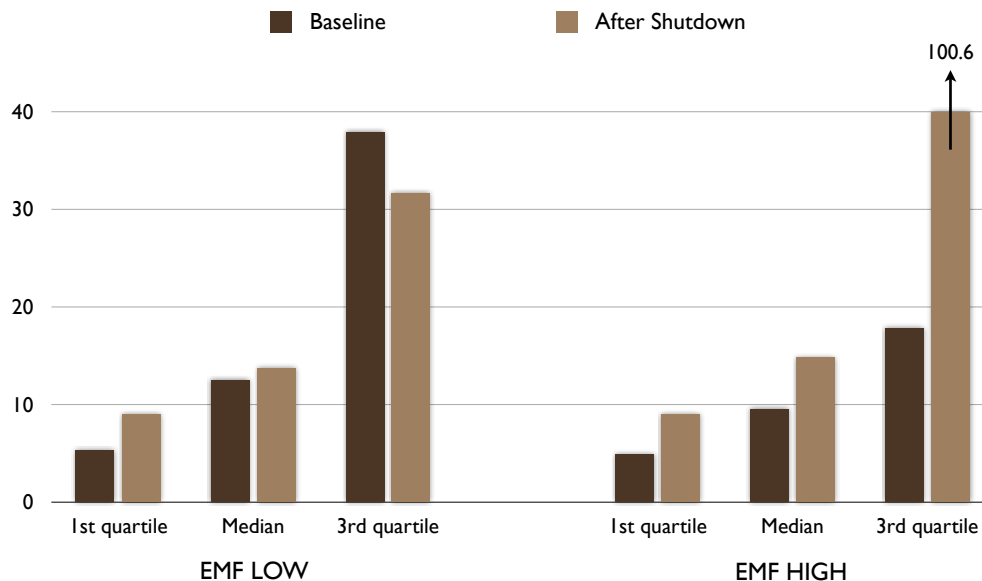
Schwarzenburg experiment: Decommissioning the Swiss national short-wave radio transmitter of Schwarzenburg, about 20 km south of the Swiss Capital city of Berne, transmitting since 1939. It operated at frequencies of 3 to 30 MHz, with a maximum power of two times 150 kW.

Figure 1. Map of the Schwarzenburg area showing the location of the transmitter, the H-field measurement points and the location of the zones A, B, C and R. The diameters of the circles around the measurement points indicate the 24 hour average magnetic field strengths, as measured between August 1992 and August 1993. (Reproduced with approval from swisstopo (BA046633.))

Abelin T, Altpeter E, Roosli M. Sleep Disturbances in the Vicinity of the Short-Wave Broadcast Transmitter Schwarzenburg. *Somnologie* (2005); 9:203-209.

Altpeter ES, Roosli M, Battaglia M, Pfluger D, Minder CE, Abelin T. Effect of short-wave (6-22 MHz) magnetic fields on sleep quality and melatonin cycle in humans: the Schwarzenburg shut-down study. *Bioelectromagnetics* (2006); 27(2):142-150.

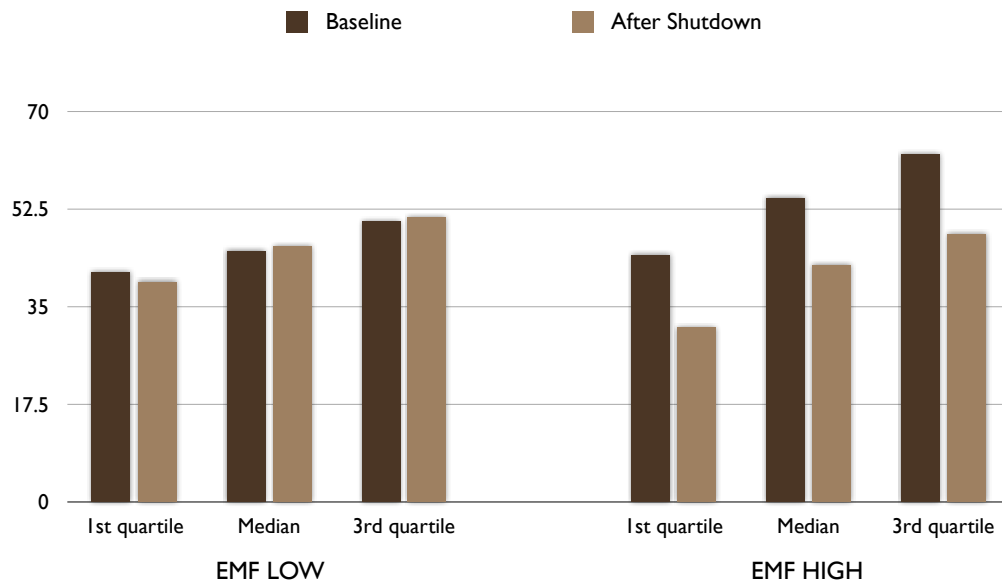
## Melatonin Excretion (pg/ml)



Altpeter ES, Roosli M, Battaglia M, Pfluger D, Minder CE, Abelin T. Effect of short-wave (6-22 MHz) magnetic fields on sleep quality and melatonin cycle in humans: the Schwarzenburg shut-down study. *Bioelectromagnetics* (2006); 27(2):142-150.



Comments on Notice of Inquiry, ET Docket No. 13-84  
**Morning Fatigue (0 - 100 Scale)**



Altpeter ES, Roosli M, Battaglia M, Pfluger D, Minder CE, Abelin T. Effect of short-wave (6-22 MHz) magnetic fields on sleep quality and melatonin cycle in humans: the Schwarzenburg shut-down study. *Bioelectromagnetics* (2006); 27(2):142-150.

Prenatal & Children; Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice. Scientific Reports. (Aldad, Taylor et al); 2012



SUBJECT AREAS:  
DEVELOPMENT  
PATTERN FORMATION  
BIOPHYSICS  
ANIMAL BEHAVIOUR

Received  
13 July 2011

Accepted  
17 February 2012

Published  
15 March 2012

Correspondence and  
requests for materials  
should be addressed to  
H.S.T. (hugh.taylor@  
yale.edu)

# Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice

Tamir S. Aldad<sup>1,2</sup>, Geliang Gan<sup>2</sup>, Xiao-Bing Gao<sup>2,3</sup> & Hugh S. Taylor<sup>1,2,4</sup>

<sup>1</sup>Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, CT 06520, <sup>2</sup>Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, <sup>3</sup>Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT 06520, <sup>4</sup>Environment and Human Health, New Haven, CT.

Neurobehavioral disorders are increasingly prevalent in children, however their etiology is not well understood. An association between prenatal cellular telephone use and hyperactivity in children has been postulated, yet the direct effects of radiofrequency radiation exposure on neurodevelopment remain unknown. Here we used a mouse model to demonstrate that *in-utero* radiofrequency exposure from cellular telephones does affect adult behavior. Mice exposed *in-utero* were hyperactive and had impaired memory as determined using the object recognition, light/dark box and step-down assays. Whole cell patch clamp recordings of miniature excitatory postsynaptic currents (mEPSCs) revealed that these behavioral changes were due to altered neuronal developmental programming. Exposed mice had dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex. We present the first experimental evidence of neuropathology due to *in-utero* cellular telephone radiation. Further experiments are needed in humans or non-human primates to determine the risk of exposure during pregnancy.

To date, 3–7% of school-aged children suffer from attention deficit hyperactivity disorder (ADHD)<sup>1</sup>. Children diagnosed with ADHD are at greater risk for low academic achievement, poor school performance, and delinquent behavior inconsistent with their developmental level<sup>2,3</sup>. The diagnosis of ADHD has increased at an average rate of 3% per year since 1997, making the condition a growing public health concern<sup>1</sup>. The behavioral problems in ADHD have been associated with neuropathology localized primarily to the prefrontal cortex. Children with ADHD have a reduction in prefrontal cortex volume, a reduction in gray and white matter, and asymmetry<sup>4,5</sup>. These children also have a deficit in working memory associated with inattention and controlled by activity of neurons in the prefrontal cortex<sup>6</sup>. A recent study showed that poor attention and low working memory capacity may be due to the inability to override the involuntary capture of attention by irrelevant information<sup>7</sup>. This too is controlled by the prefrontal cortex, as the shifting of one's attention voluntarily is driven by “top-down” signals in the prefrontal cortex while the involuntary capture of attention depends on “bottom-up” signals from both subcortical structures and the visual cortex<sup>7</sup>.

The etiology of ADHD remains unknown and growing evidence suggests that it is not solely due to genetic factors<sup>8</sup>. Risk factors include family psychiatric history, socioeconomic status, gender, and smoking during pregnancy<sup>9,10</sup>. A recent epidemiologic study found an association between prenatal cellular telephone exposure and subsequent behavioral problems in the exposed offspring<sup>11</sup>. This association is important given the increasing number of cellular phone users worldwide, reaching approximately four billion as of December 2008<sup>12</sup>. However, evidence of direct causation is lacking.

The specific absorption rate (SAR) is a measure of tissue radiation exposure. The European Union has set a SAR limit of 2.0 W/kg and in the United States this limit is set at 1.6 W/kg<sup>13</sup>. The *in-utero* effects of radiation exposure



within this SAR limit on neurodevelopment remain unknown. To determine if prenatal exposure to radiofrequency radiation leads to impaired memory or behavior after birth, we performed behavioral and electrophysiological studies in mice exposed *in-utero* to 800–1900 Mhz radiofrequency radiation from cellular telephones.

## Results

In order to determine if *in-utero* cell phone radiation exposure affects behavior we chose to conduct a battery of tests that identify impairments in memory, hyperactivity, anxiety, and fear, which are often associated with ADHD. Thirty-three female mice were exposed throughout gestation (days 1–17) to radiation from muted and silenced 800–1900 Mhz cellular phones with a SAR of 1.6 W/kg. The phones were positioned above each cage over the feeding bottle area at a distance of 4.5–22.3 cm from each mouse, depending on the location of the animal within the cage, and placed on an uninterrupted active call for the duration of the trial. A control group of forty-two female mice was kept concurrently under the same conditions, however using a deactivated phone. Parturition was not different between groups and occurred at 19 days  $\pm$  1 day. In order to evaluate memory in the exposed and unexposed mice, 161 progeny were given a standard object recognition memory test in three different cohorts at 8, 12, and 16 weeks of age (82 experimental and 79 control mice). The mice were allowed to explore two identical objects for 15 minutes per day for two days and on the third day one object was replaced with a novel object. On day 3 the mice were filmed for 5 minutes exploring the novel and familiar objects. Three observers, blinded to the treatment, viewed the footage and recorded the exploration time for the novel and familiar objects. The preference index was defined as the time spent exploring the new object divided by the time spent exploring both the new and old object, multiplied by one hundred. A decrease in preference index indicates diminished memory. The preference index of the experimental group at 8, 12, and 16 weeks was less than the control and the results were significant at each time point [Figure 1]. The mean preference index in the exposed group was 56.8, 69.4 and 63.5 compared to 66.5, 71.7, and 71.2 in the control group at 8, 12 and 16 weeks, respectively. The experimental group had a cumulative mean preference index of 63.0% and the control group 69.9% ( $p = 0.003$ ,  $n=161$ ,  $t$  test). Compared to the control group, the exposed mice had a significantly lower mean preference index suggesting impairment in memory [Figure 1]. In order to ensure that our findings are in fact due to memory deficits and not distractibility or hyperactivity we calculated the percent time spent idle - not exploring either of the objects. The mean idle time in the exposed group was 90.06, 90.53, and 96.48 compared to 92.12, 91.89, and 97.07 in the control group at 8, 12 and 16 weeks, respectively. The control group had a cumulative mean idle time of 90.8% while the experimental group had a cumulative mean idle time of 90.4% and the difference between the two groups was not statistically significant ( $p = .58$ ).

To explore fearful behavior we performed the light/dark box test measuring hyperactivity/anxiety and the step down assay assessing fear of exploring the environment. The light/dark box test measures anxiety using a rodent's natural aversion to bright light<sup>14</sup>. The box contained two compartments: one white compartment that was illuminated and one black compartment that remained dark. The number of transitions between the two compartments was used to determine locomotion and in turn hyperactivity<sup>15</sup>. Anxious behavior is measured by recording the time spent in each compartment<sup>15</sup>. A total of 141 progeny were given the light/dark box test in three different cohorts at 12, 15, and 18 weeks of age (71 experimental and 70 control mice). Each mouse was placed in the light/dark box for 5 minutes and filmed. Three observers, blinded to the treatment regimen, viewed the footage and recorded the time spent in the dark compartment along with the number of transitions between each compartment. The

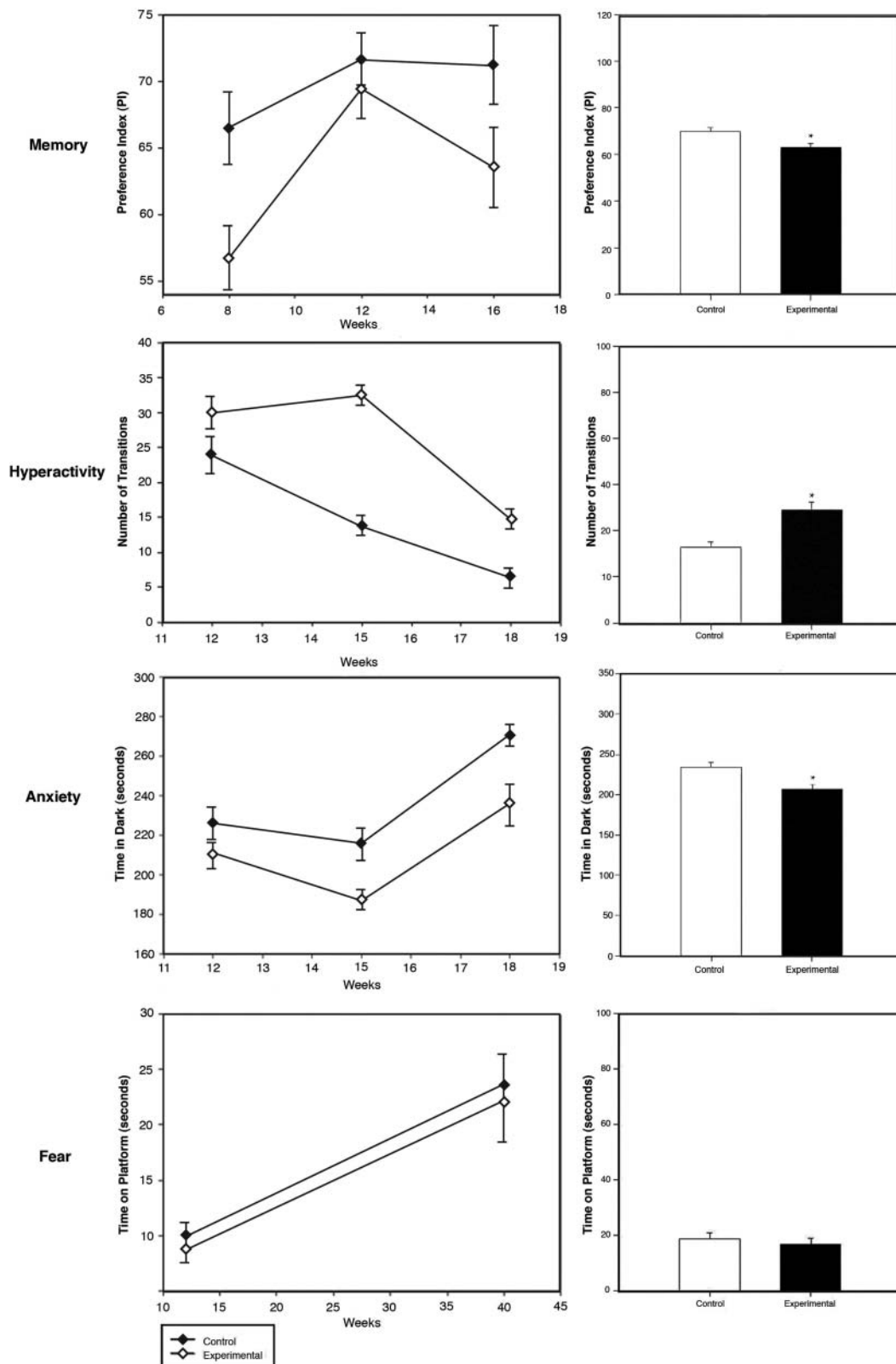
average number of transitions in the experimental group at 12, 15, and 18 weeks was fewer than in respective controls and the results were significant at each time point [Figure 1]. The average number of transitions in exposed mice was 29.9, 32.5 and 14.8 compared to 23.9, 13.8, and 6.5 in the control group at 12, 15 and 18 weeks, respectively. The experimental group showed a cumulative mean of 24.4 transitions and the control group showed a mean of 16.4 transitions ( $p < 0.001$ ). Compared to the control group, the greater number of transitions between the two compartments in the experimental group suggested hyperactive behavior [Figure 1].

To identify whether anxiety might be a factor contributing to the behavioral phenotype reported in the light/dark box experiment, we first compared the duration of time in the dark versus the time spent in the light. An increased time in the dark indicates anxious behavior<sup>15</sup>. At 12, 15, and 18 weeks the experimental group spent less time in the dark and the results were significant at each time point [Figure 1]. The duration of time in darkness of the exposed group was 210.8, 187.0 and 235.8 seconds compared to 225.6, 215.5 and 270.6 seconds in the control group at 12, 15 and 18 weeks, respectively. The mice exposed *in utero* spent a cumulative average of 207 seconds in the dark while the control mice spent an average of 234 seconds in the dark indicating decreased anxiety in the cellular phone exposed mice ( $p < 0.001$ ) [Figure 1].

The Step Down Assay was performed on 98 mice at 12 weeks and in adulthood to determine fear of exploring the environment (51 control and 47 experimental mice). The test is performed by recording the time spent on a standard platform. A greater period of time on the platform indicates increased fearfulness. Exposed mice showed no significant difference in time spent on the platform when compared to the controls [Figure 1]. The control mice spent an average of 18.5 seconds while the experimental group spent an average of 16.7 seconds ( $p = 0.59$ ) [Figure 1].

Overall, the mice exposed *in-utero* to radiation were hyperactive, had decreased memory, and decreased anxiety.

To understand the mechanisms underlying the changes in the memory and hyperactivity in animals exposed to radiation *in-utero*, we examined whether changes in the neuronal circuitry occurred in brain areas responsible for these compromised behaviors. Specifically, we asked whether changes in the synaptic transmission in CNS neurons are responsible for impaired memory and hyperactivity in radiation-exposed animals. The prefrontal cortex (PFC) is responsible for executive functions by screening distractions and maintaining attention in goal-oriented behaviors. Impairment of the PFC leads to dysregulated behavior/emotion such as ADHD<sup>16</sup>. The pyramidal neurons, the primary cell type in this structure, regulate attention and behavior through a complex and interconnected network. Whole cell patch clamp recordings of miniature excitatory postsynaptic currents (mEPSCs) were performed in pyramidal neurons of the PFC in control and cell phone-exposed mice. mEPSCs were generated by random vesicle release of glutamate from presynaptic neurons in the absence of stimulation. The measurement of mEPSCs is used to analyze the efficacy of synaptic transmission. Changes in mEPSC frequency are thought to result from modification of the presynaptic component of synaptic transmission, while amplitude changes indicate alterations in the postsynaptic component<sup>17,18</sup>. Coronal prefrontal cortex slices (300  $\mu$ m) were prepared from 3–4 week old mice. mEPSCs were recorded in layer V pyramidal neurons in the prefrontal cortex in mice exposed to *in-utero* radiation for 9, 15 and 24 hours/day throughout gestation; the detection and analysis of mEPSC frequency and amplitude were performed as we described previously<sup>18</sup>. In animals exposed to *in-utero* radiation for 24 hours/day, a decrease in the frequency of mEPSCs was seen (control:  $1.00 \pm 0.12$  Hz,  $n = 40$ ; 24 hours/day:  $0.72 \pm 0.06$  Hz,  $n = 43$ ,  $p < 0.05$ ,  $t$  test, Figure 2A and B). The cumulative probability curves for the amplitude of mEPSC events recorded from the *in utero* cell phone-exposed mice (24 hours/day) shifted



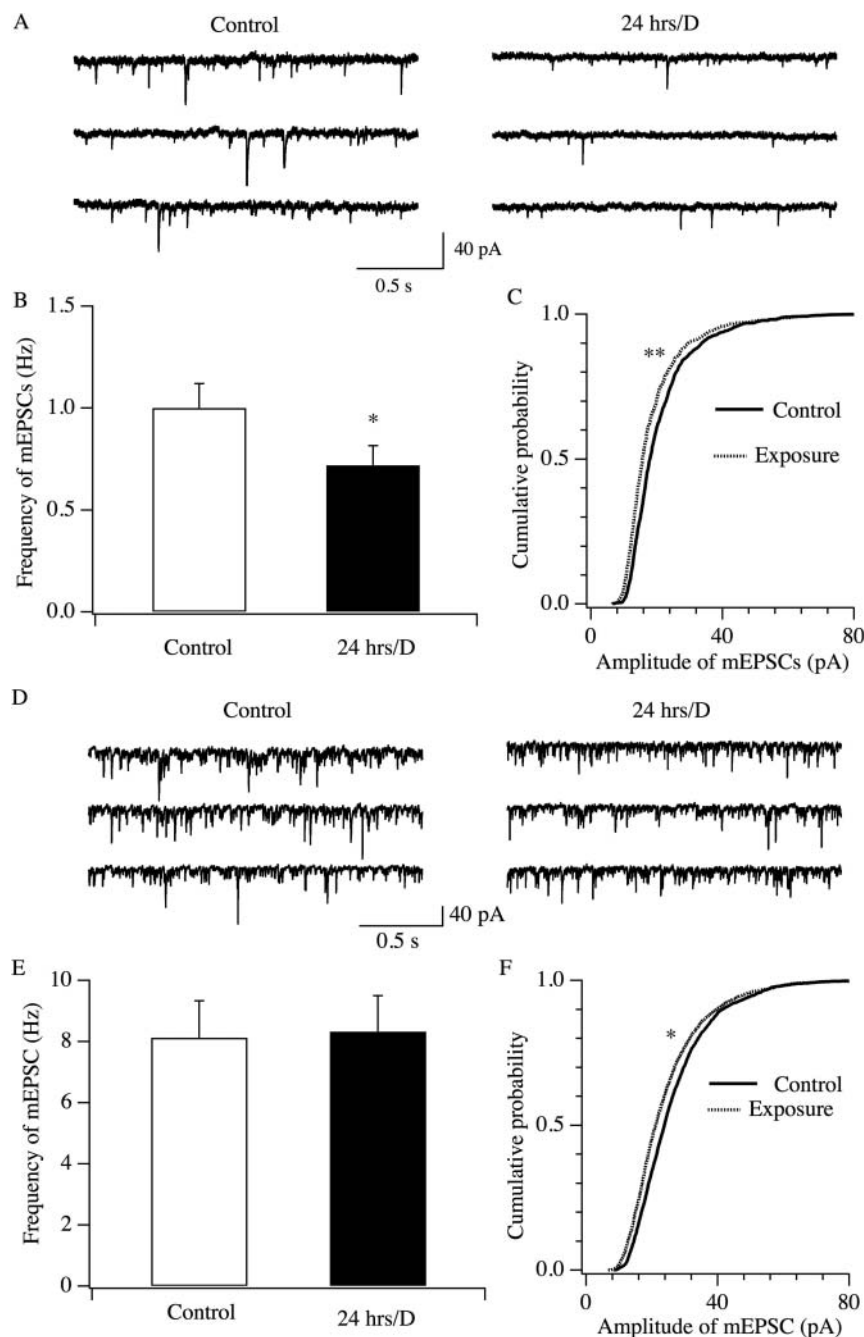
**Figure 1 | Behavioral testing in exposed and control mice.** The left column displays the data determined in mice at several ages after exposure. The right column demonstrates the cumulative average. To test memory the Standard object recognition memory test was used and a Preference Index (percent of total exploration time spent exploring the new object) shown at 8, 12, and 16 weeks of age. The cumulative mean preference index of the experimental group was 63.0% and the control group 69.9% (\* $p = 0.003$ ,  $n = 161$ ). To test hyperactivity we used the Light/Dark box test and display transitions at 12, 15, and 18 weeks of age. The cumulative mean number of transitions in the experimental group was 24.4 and the control group 16.4 (\* $p < 0.001$ ,  $n = 141$ ). To test anxiety we measured time spent in the dark at 12, 15, and 18 weeks of age. The cumulative average time spent in the dark in the experimental group was 207 seconds and in the control was 234 seconds (\* $p < 0.001$ ,  $n = 141$ ). To measure fear we used the Step down assay and display the time spent on the platform at 12 weeks and adulthood. The cumulative mean time spent on the platform in the experimental group was 16.7 seconds and in the control was 18.5 seconds ( $p = 0.59$ ,  $n = 98$ ).



significantly to the left relative to those recorded from the controls ( $P < 0.01$ , Kolmogorov-Smirnov test; control: 2765 events, cell phone exposure: 2224 events), indicating that the amplitude of mEPSCs was decreased [Figure 2C]. In a subset of experiments, we examined whether the reduction of mEPSC frequency depended on dosages of exposure in mice prenatally exposed 0, 9, 15 and 24 hours per day [Figure 3]. The trend of the dose-dependent decrease in the frequency of mEPSCs (0 hour/day:  $1.37 \pm 0.41$ ,  $n = 9$ ; 9 hours/day:  $1.27 \pm 0.21$  Hz,  $n = 9$ ; 15 hours/day:  $1.04 \pm 0.20$  Hz,  $n = 10$ ; 24 hours/day:  $0.72 \pm 0.13$ ,  $n = 11$ ) was statistically significant (linear correlation: Correlation Coef =  $-0.97$ , Unadjusted  $r^2 = 0.94$ ,  $P < 0.05$ ).

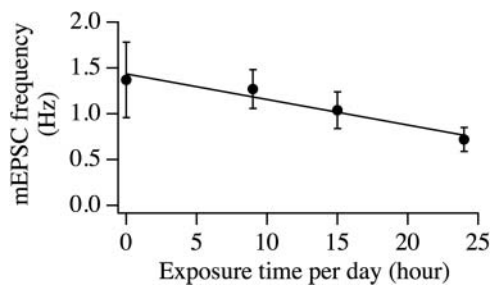
Altogether, these results indicate that synaptic efficacy of glutamatergic transmission decreases at both pre- and postsynaptic sites in layer V pyramidal neurons. Thus, we demonstrate impairment in glutamatergic transmission (release from nerve terminals and glutamate receptor response) onto pyramidal neurons in the PFC after *in-utero* exposure to radiation from cellular telephones.

In a parallel experiment we examined whether *in-utero* radiation exposure led to changes in synaptic transmission in another brain area. mEPSCs were recorded in neurons in the ventral medial hypothalamus (VMH), a brain area implicated in the regulation of energy homeostasis<sup>19,20</sup>. Our results indicated that in mice exposed to radiation for 24 hours/day, the frequency of mEPSCs (control:



**Figure 2 | Synaptic efficacy of glutamatergic synapses is decreased in brain neurons of mice after prenatal exposure to cell phone radiation.** A–C, mEPSCs were recorded in layer V pyramidal neurons of the prefrontal cortex. Representative traces of mEPSCs from control and cell phone exposure groups are shown in A. mEPSC frequency and cumulative probability of mEPSC amplitude from both groups are shown in B (\*,  $P < 0.05$ , t test) and C (\*\*,  $P < 0.01$ , Kolmogorov-Smirnov test; controls, 2225 events; Exposed, 2766 events). D–F, representative traces, frequency and amplitude of mEPSCs recorded in neurons in the VMH are shown. \*,  $P < 0.05$ , Kolmogorov-Smirnov test; Control: 2161 events, Cell phone group: 2261 events.





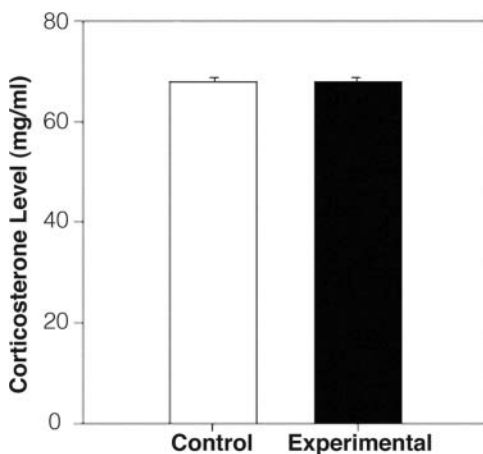
**Figure 3** | A dose-dependent attenuation in the frequency of mEPSCs in layer V pyramidal neurons in mice. The frequency of mEPSCs recorded in mice prenatally exposed to cell phone radiation at of dose of 0, 9, 15 and 24 hrs per day are shown. Error bars are SEM. The dose responsive relationship is determined using regression analysis (Correlation coefficient,  $-0.97$ ;  $r^2$ ,  $0.94$ ;  $P < 0.05$ ).

$8.13 \pm 1.20$  Hz,  $n = 14$ ; cell phone radiation:  $8.32 \pm 1.17$  Hz,  $n = 14$ ) was not significantly different from that in control mice ( $P > 0.05$ ,  $t$  test, Figure 2D and E). However, the cumulative probability of mEPSC amplitude recorded in radiation-exposed mice significantly shifted to the left ( $P < 0.05$ , Kolmogorov-Smirnov test; control: 2161 events, cell phone group: 2261 events; Figure 2F), suggesting that the amplitude of mEPSCs is smaller in the cell-phone exposed group than in controls. This result implies that an impairment of glutamatergic transmission occurs at the postsynaptic site. In summary, our results suggest that the effects of prenatal exposure to the cell phone radiation were not limited to the cortex.

Maternal stress can alter fetal development by increasing offspring exposure to corticosterone, causing cognitive deficits, hyperactivity, and alterations of the hypothalamo-pituitary-adrenal axis<sup>21</sup>. In order to exclude the possibility that impaired memory and behavior in exposed mice was caused by stress resulting from experimental manipulation, we measured serum corticosterone levels on day twelve of gestation using an ELISA assay. The mean corticosterone level in the exposed female mice ( $69.91$  ng/ml,  $n = 6$ ) was not significantly different from that in the control females ( $69.94$  ng/ml,  $n = 6$ ) [Figure 4], eliminating stress as a source of the observed behavioral and electrophysiologic differences.

## Discussion

Here we demonstrate that fetal exposure to 800–1900 Mhz-rated radiofrequency radiation from cellular telephones leads to behavioral and neurophysiological alterations that persist into adulthood. Mice



**Figure 4** | Corticosterone levels during pregnancy were unaltered by exposure. The mean corticosterone level in the pregnant control females was  $69.94$  ng/ml and in the exposed female mice was  $69.91$  ng/ml.

exposed during pregnancy had impaired memory, were hyperactive, and had decreased anxiety, indicating that *in-utero* exposure to radiofrequency is a potential cause of neurobehavioral disorders. We further demonstrated impairment of glutamatergic synaptic transmission onto pyramidal cells in the prefrontal cortex associated with these behavioral changes, suggesting a mechanism by which *in-utero* cellular telephone radiation exposure may lead to the increased prevalence of neurobehavioral disorders.

This is the first study to specifically identify effects of radiofrequency exposure on the mouse fetus. During critical windows in neurogenesis the brain is susceptible to numerous environmental insults; common medically relevant exposures include ionizing radiation, alcohol, tobacco, drugs and stress. The effects of these agents are dependent on dose and timing of exposure. Even small exposures during periods of neurogenesis have a more profound effect than exposure as an adult. Alcohol affects cerebral neurogenesis, patterning of brain development and subsequent behavior. Maternal smoking also affects fetal development; fetal tobacco exposure results in a higher incidence of behavioral and cognitive impairment including ADHD. Similarly, prenatal exposure to cocaine can lead to behavioral disorders. Even prenatal maternal stress can lower intelligence and language abilities in offspring. As demonstrated by these examples, environmental exposures occurring in fetal life can lead to persistent neurological deficits. Exposure to these insults as an adult does not carry the same consequences. It is therefore not surprising that studies exposing adult animals to radiofrequency radiation failed to find similar significant defects in behavior. The exposure to cellular telephones in pregnancy may have a comparable effect on the fetus and similar implications for society as do exposures to other common neurodevelopmental toxicants. While this data demonstrates a clear association between fetal EMR exposure and neurodevelopment, it is important to recognize that the extrapolation of this animal model to humans is limited; the exposures used here are not identical to those experienced by the human fetus.

The molecular and cellular effects of radiofrequency exposure are not yet fully characterized. Multiple targets have been identified *in vitro*. Electromagnetic frequency exposure has been demonstrated to affect cell division and proliferation, both by inducing apoptosis and altering the cell cycle<sup>22</sup>. Electromagnetic radiation may promote the formation of reactive oxygen species (ROS) causing cell damage<sup>23</sup>. One study specifically analyzing the effects of radiofrequency radiation on glioma cells demonstrated altered oxidative stress, a potential mediator of the alterations caused by electromagnetic radiation<sup>24</sup>. Electromagnetic frequency radiation has also been found to activate ERK and p38 MAPK signaling<sup>25</sup>. Although the precise molecular mechanisms that led to altered glutamatergic synaptic transmission in the prefrontal cortex identified in this study are not yet fully known, here we provide the first evidence that links changes in neuronal circuitry centered on layer V pyramidal neurons in the PFC with impaired memory and cognitive behaviors in animals exposed to radiation from cellular phone use. Our results indicate that the release of glutamate from the nerve terminals on PFC neurons and response of PFC neurons to glutamate are impaired in mice prenatally exposed to cell phone radiation. These results are consistent with previous reports that compromised glutamatergic transmission onto PFC neurons underlies impaired memory and cognitive functions in animals<sup>26,27</sup>. Our results also imply that the effects of prenatal exposure to radiation on the brain might be global, since glutamatergic transmission onto neurons in another area of the brain (i.e., the VMH) was decreased as well. The effects of prenatal exposure to cell phone radiation may have more profound effects on brain functions than reported in this study. However, the effect was not identical; there are likely to be cell type specific or regional variations in susceptibility. Alternatively, the depth of the VMH may have shielded this region from maximal exposure.





Given the recent advancements in the technology of cellular telephones (i.e. smart phones), they are now used in a capacity beyond that of a basic telephone. For many, cellular telephones are used as a bedside alarm clock and personal organizer. Cellular telephone usage can reach 24 hours/day, leaving users increasingly exposed to the potentially harmful effects of radiofrequency radiation exposure. Our findings indicated significant electrophysiological and behavioral changes in mice exposed *in-utero* to radiation. The significant trend between the groups treated for 0, 9, 15, and 24 hours/day demonstrates that the effects are directly proportional to usage time, and suggests that safety limits, particularly for pregnant women, can be established. Though it is difficult to translate these findings to human risks and vulnerability, we identify a novel potential contribution to the increased prevalence in hyperactive children, one that is easily prevented. However, it is important to note that hyperactivity and anxiety are closely related and my confound one another.

In this study we used cellular telephones as a source of EMR to mimic human exposure. However there are several limitations to this study that include lack of a defined exposure from a traditional EMF generator. Further we did not measure the level of exposure and the distance to the source was not fixed; mice were free to move within the confines of the cage. Power density measurements with respect to orientation, polarization, reflection, and interference were not considered. In order to determine the maximal effects and potential risks associated with exposure, the mice were exposed from conception to birth, however mouse brain development is incomplete at birth and distinct from that of humans. While neurological effects were found here, future studies should focus on a more narrow gestational age of exposure, use EMF generators to more precisely define exposure, and limit variation in the distance from the source. Definitive studies in humans are required prior to extrapolating these behavioral findings to humans.

In summary, we demonstrate that fetal radiofrequency radiation exposure led to neurobehavioral disorders in mice. We anticipate these findings will improve our understanding of the etiology of neurobehavioral disorders. The rise in behavioral disorders in developed countries may be, at least in part, due to a contribution from fetal cellular telephone radiation exposure. Further testing is warranted in humans and non-human primates to determine if the risks are similar and to establish safe exposure limits during pregnancy.

## Methods

**Exposure and Behavioral Tests.** Over five separate experiments, a total of 27 breeding cages were set-up each containing 3 CD-1 female mice and 1 CD-1 male mouse (13 experimental cages and 14 control cages). Each experimental cage was equipped with a muted and silenced 800–1900 Mhz cellular phone with a SAR of 1.6 W/kg placed over the feeding bottle area at a distance of 4.5–22.3 cm from the mice. The cellular phones were then placed on an active call for 24 hours per day and the 33 experimental female mice were exposed throughout gestation (days 1–17). An additional six females were exposed to an active phone for either 9 or 15 hours per day. Each control cage was equipped with a deactivated phone and was kept under the same conditions. To assure equal exposure time independent of the variable length of gestation (18–20 days), at the end of day 17 all phones were removed. On day 18 all female mice were separated and placed in their own cage yielding a total of 39 exposed pregnant females and 42 unexposed pregnant females. Throughout the experiment, both the control and experimental mice were fed and given water *ad libitum*. The mice were maintained on a 12 hour light/dark cycle (07:00 on) and all procedures were approved by the Yale University Animal Care and Use Committee.

Memory was evaluated using a standard object recognition memory test. A total of 161 pups were tested (82 experimental mice and 79 control mice) at 8, 12, and 16 weeks. The test consisted of two learning days (Day 1 and 2) and one test day (Day 3). On Day 1 four opaque exploration chambers were set-up in the exam room at a luminosity of 420–440 Lux. Prior to conducting each test, the mice were placed in the testing room and allowed 1 hour to acclimate to the light. Two identical objects were then placed in each of the four chambers and a single mouse was placed in each chamber to explore the two identical objects for 15 minutes. Before repeating the experiment, the objects and the chambers were cleaned thoroughly with a detergent solution to remove any scents or odors. On Day 3 a video camera was placed over all 4 chambers and the objects were rearranged so that each chamber had one familiar object and one novel object. The mice were then allowed to explore both objects and were filmed for 5 minutes. Upon completing the experiment, 3 observers, blinded to

the treatment regimen, viewed the first 2 minutes of footage to determine the time spent exploring the novel object. Exploration of the new object was defined as sniffing at less than 1 cm. A preference index was then calculated by dividing the time spent exploring the new object by the total exploration time multiplied by one hundred. The percent time spent idle - not exploring either of the objects was also calculated in order to ensure that our findings are in fact due to memory deficits and not distractibility or hyperactivity.

The light-dark box test was conducted using a light-dark box, constructed of black and white Plexiglass (45×27×27 cm). The dark compartment (18×27 cm) was made of black Plexiglass with a black Plexiglass cover and the light compartment (27×27 cm) was made of white Plexiglass and remained open. The light compartment was kept at a luminosity of 420–440 Lux. An opening (7.5×7.5 cm) was located in the wall between the two chambers allowing free access between the light and dark compartments. A video camera was then placed over the box for filming. Prior to conducting each test, the mice were placed in the testing room and allowed 1 hour to acclimate to the light. A single mouse was then placed in the light chamber and was allowed to explore the box for 5 minutes while being filmed. Before repeating the experiment, the chambers were cleaned thoroughly with a detergent solution to remove any scents or odors. Three observers, blinded to the treatment regimen, then viewed the footage and recorded the total time spent in the dark as well as the total number of transitions. This data was then interpreted as described in the text to analyze anxiety and hyperactivity.

The Step Down Assay was performed to determine fearful behavior by placing a mouse gently on a platform (96 well plate) and recording the time on the platform. The timer was stopped once the mouse stepped off the platform with all four paws. Before repeating the experiment, the platform was cleaned thoroughly with a detergent solution to remove any scents or odors.

**Corticosterone Measurement.** Gestational stress was analyzed by collecting serum on Day 12 of gestation from 6 exposed and 6 unexposed pregnant females. Serum samples were tested for corticosterone levels using an enzyme immunoassay kit (Assay Designs, Ann Arbor, MI) as recommended by the manufacturer.

**Electrophysiology.** Mice from control and cell phone-exposed groups were anesthetized with ether and then decapitated. The brains were rapidly removed and immersed in an oxygenated cutting solution at 4°C containing (in mM): sucrose 220, KCl 2.5, CaCl<sub>2</sub> 1, MgCl<sub>2</sub> 6, NaH<sub>2</sub>PO<sub>4</sub> 1.25, NaHCO<sub>3</sub> 26, and glucose 10, and adjusted to pH 7.3 with NaOH. Coronal cortical slices (300 μm thick) were prepared from the prefrontal area of the brain and the ventral medial hypothalamus (VMH) using a vibratome. After preparation, slices were maintained in a holding chamber with artificial cerebrospinal fluid (ACSF) (bubbled with 5% CO<sub>2</sub> and 95% O<sub>2</sub>) containing (in mM): NaCl 124, KCl 3, CaCl<sub>2</sub> 2, MgCl<sub>2</sub> 2, NaH<sub>2</sub>PO<sub>4</sub> 1.23, NaHCO<sub>3</sub> 26, glucose 10, pH 7.4 with NaOH, and were transferred to a recording chamber constantly perfused with bath solution (33°C) at 2 ml/min after at least a 1 hr recovery.

Whole-cell voltage clamp (at −60 mV) was performed to observe miniature excitatory postsynaptic currents (mEPSCs) in layer V cortical neurons with a Multiclamp 700 A amplifier (Molecular devices, CA). The patch pipettes (tip resistance = 4–6 MΩ) were made of borosilicate glass (World Precision Instruments) with a pipette puller (Sutter P-97) and back filled with a pipette solution containing (in mM): K-gluconate 135, MgCl<sub>2</sub> 2, HEPES 10, EGTA 1.1, Mg-ATP 2, Na<sub>2</sub>-phosphocreatine 10, and Na<sub>2</sub>-GTP 0.3, pH 7.3 with KOH. mEPSCs were recorded in pyramidal neurons under voltage clamp (at −60 mV) in the presence of tetrodotoxin (TTX, 0.5 μM), and a GABA-A receptor antagonist picrotoxin (50 μM). Both input resistance and series resistance were monitored constantly during experiments. The series resistance (between 20 and 40 MΩ) was partially compensated by the amplifier and only recordings with stable series and input resistance throughout experiments were accepted. All data were sampled at 3–10 kHz and filtered at 1–3 kHz with an Apple Macintosh computer using Axograph X (AxoGraph Scientific). mEPSC events were detected and analyzed with AxoGraph X and plotted with Igor Pro software (WaveMetrics, Lake Oswego, OR) as described previously by Rao, et al (2007). Linear correlation was performed with the software GB-STAT (Dynamic Microsystems, Inc, Silver Spring, MD).

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders* (2000) Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association.
2. Barkley, R. Behavioral Inhibition, Sustained Attention, and Executive Functions: Constructing a Unifying Theory of ADHD. *Psychol Bull* **121**, 65–94 (1997).
3. Rappley, M. Attention deficit-hyperactivity disorder. *N Engl J Med* **352**, 165–73 (2005).
4. Sowell, E. R. Cortical abnormalities in children and adolescent with attention-deficit hyperactivity disorder. *Lancet* **362**, 1699–707 (2003).
5. Castellanos, F. X. Development trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* **288**, 1740–48 (2002).
6. Castellanos, F. X. & Tannock, R. Neuroscience of attention deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* **3**, 617–28 (2002).
7. Fukuda, K. & Vogel, E. K. Human variation in overriding attentional capture. *J Neurosci* **29**, 8726–33 (2009).
8. Singh, I. Beyond polemics: science and ethics of ADHD. *Nat Rev Neurosci* **9**, 957–64 (2008).



9. Brasset-Harknett, A. & Butler, N. Attention-deficit/hyperactivity disorder: an overview of the etiology and a review of the literature relating to the correlates and lifecourse outcomes for men and women. *Clin Psychol Rev.* **27**, 188–210 (2007).
10. Biederman, J. & Faraone, S. V. Attention-deficit hyperactivity disorder. *Lancet* **366**, 237–248 (2005).
11. Divan, H. Kheifets, L. Obel, C. & Olsen, J. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. *Epidemiology* **19**, 523–529 (2008).
12. Measuring the Information Society: The ICT Development Index. International Telecommunication Union. p108. (2009).
13. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). International Commission on Non-Ionizing Radiation Protection. *Health Phys.* **74**, 494–522 (1998).
14. Bourin, M. & Hascoet, M. The mouse light/dark box test. *Eur J Pharmacol.* **463**, 55–65 (2003).
15. Corbetta, S. *et al.* Hyperactivity and novelty-induced hyperactivity in mice lacking Rac3. *Behav Brain Res* **186**, 246–255 (2008).
16. Arnsten, A. F. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci* **10**, 410–22 (2009).
17. Ungless, M. A., Whistler, J. L., Malenka, R. C. *et al.* Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature*. **411**, 583–587 (2001).
18. Rao, Y. *et al.* Prolonged wakefulness induces experience-dependent synaptic plasticity in mouse hypocretin/orexin neurons. *J Clin Invest.* **117**, 4022–33 (2007).
19. López, M. *et al.* Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. *Nat Med.* **16**, 1001–8 (2010).
20. Xu, Y. *et al.* PI3K signaling in the ventromedial hypothalamic nucleus is required for normal energy homeostasis. *Cell Metab.* **12**, 88–95 (2010).
21. Koehl, M., Lemaire, V., Le Moal, M. & Abrous, D. N. Age-dependent effect of prenatal stress on hippocampal cell proliferation in female rats. *Eur J Neurosci.* **29**, 635–40 (2009).
22. Panagopoulos, D. J., Chavdoula, E. D., Nezis, I. P. & Margaritis, L. H. Cell death induced by GSM 900-MHz and DCS 1800-MHz mobile telephony radiation. *Mutat Res.* **626**, 69–78 (2007).
23. Zmysłony, M. *et al.* Acute exposure to 930 MHz CW electromagnetic radiation in vitro affects reactive oxygen species level in rat lymphocytes treated by iron ions. *Bioelectromagnetics.* **25**, 324–8 (2004).
24. Cao, Y. *et al.* 900-MHz microwave radiation enhances gamma-ray adverse effects on SHG44 cells. *J Toxicol Environ Health A.* **72**, 727–32 (2009).
25. French, P. W., Penny, R., Laurence, J. A. & McKenzie, D. R. Mobile phones, heat shock proteins and cancer. *Differentiation* **67**, 93–97 (2001).
26. Jentsch, J. D. *et al.* Dysbindin modulates prefrontal cortical glutamatergic circuits and working memory function in mice. *Neuropsychopharmacology.* **34**, 2601–8 (2009).
27. Rubino, T. *et al.* The depressive phenotype induced in adult female rats by adolescent exposure to THC is associated with cognitive impairment and altered neuroplasticity in the prefrontal cortex. *Neurotox Res.* **15**, 291–302 (2009).

## Acknowledgements

The authors thank Arie Kaffman and Richard Hochberg for critical reading of the manuscript and thank Neil Odem, Michael Lee and Yuzhe Feng for their technical assistance and analysis of behavioral test results. Supported by grants from EHHI and NICHD (HD052668).

## Author contributions

TSA treated the mice, performed the behavioral studies, analyzed the data and wrote the manuscript. GG and XBG performed and analyzed the electrophysiology studies. HST designed the experiment, analyzed the data and edited the manuscript.

## Additional information

**Competing financial interests:** The authors declare no competing financial interests.

**License:** This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivative Works 3.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0/>

**How to cite this article:** Aldad, T.S., Gan, G., Gao, X. & Taylor, H.S. Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice. *Sci. Rep.* **2**, 312; DOI:10.1038/srep00312 (2012).

Prenatal & Children; Fetal Exposures and Cell Phones.  
Studies List. Prof. Hugh Taylor MD.; 2015

## Fetal Exposures and Cell Phones

Hugh S. Taylor MD

### RESEARCH

Aldad TS, Gan G, Gao XB, Taylor HS. (2012). [Fetal Radiofrequency Radiation Exposure From 800-1900 MHz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice](#). Scientific Reports; 2, 312.

Bas O, Odaci E, Kaplan S, Acer N. (2009). [900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in adult rat](#). Brain Research. 1265, 178–185.

Bas et al., (2009). [Chronic prenatal exposure to the 900 megahertz electromagnetic field induces pyramidal cell loss in the hippocampus of newborn rats](#). Toxicol Ind Health. 25, 377–384.

Bin Lv, Zhiye Chen, Tongning Wu, Qing Shao, Duo Yan, Lin Ma, Ke Lu, Yi Xie. (2014). [The alteration of spontaneous low frequency oscillations caused by acute electromagnetic fields exposure](#). Clin Neurophysiol. 125(2), 277-86.

Byun Y-H, Ha M, Kwon H-J, Hong Y-C, Leem J-H. (2013). [Mobile Phone Use, Blood Lead Levels, and Attention Deficit Hyperactivity Symptoms in Children: A Longitudinal Study](#). PLoS ONE. 8(3)

Deshmukh P.S. et al., 2015. [Cognitive impairment and neurogenotoxic effects in rats exposed to low-intensity microwave radiation](#). Int J Toxicol. 34(3): 284-290.

Deshmukh et al., (2013). [Effect of low level microwave radiation exposure on cognitive function and oxidative stress in rats](#). Indian J Biochem Biophys; 50(2), 114-9.

Divan HA, Kheifets L, Obel C, Olsen J. (2012). [Cell phone use and behavioural problems in young children](#). J Epidemiol Community Health. 66(6), 524-9.

Divan HA, Kheifets L, Obel C, Olsen J. (2008). [Prenatal and postnatal exposure to cell phone use and behavioral problems in children](#). Epidemiology. 19(4), 523-9.

Hao, Y.-H., Zhao, L., & Peng, R.-Y. (2015). [Effects of microwave radiation on brain energy metabolism and related mechanisms](#). Military Medical Research, 2, 4. <http://doi.org/10.1186/s40779-015-0033-6>

Júnior et al., (2014). [Behavior and memory evaluation of Wistar rats exposed to 1.8 GHz radiofrequency electromagnetic radiation](#). Neurol Res. 36(1).

Jing et al., (2012). [The influence of microwave radiation from cellular phone on fetal rat brain](#). Electromagn Biol Med. 31(1), 57-66.

Megha, K Deshmukh, PS, Banerjee, BD, Tripathi, AK, Abegaonkar, MP. (2012). [Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats](#). Indian J Experimental Biology. 50(12), 889-896.

Narayanan SN, Kumar RS, Karun KM, Nayak SB, Bhat PG., (2015) Possible cause for altered spatial cognition of prepubescent rats exposed to chronic radiofrequency electromagnetic radiation. [Metab Brain Dis](#). 2015 Oct;30(5):1193-206. doi: 10.1007/s11011-015-9689-6. Epub 2015 Jun 3.

Odaci et. al., (2015 ) [Maternal exposure to a continuous 900-MHz electromagnetic field provokes neuronal loss and pathological changes in cerebellum of 32-day-old female rat offspring](#). J Chem Neuroanat. Sep 21.

Odaci E, Bas O, Kaplan S. (2008). [Effects of prenatal exposure to a 900 megahertz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study](#). Brain Research. 1238, 224–229.

Ozgun et al., (2013) [Effects of prenatal and postnatal exposure to GSM-like radiofrequency on blood chemistry and oxidative stress in infant rabbits, an experimental study](#). Cell Biochem Biophys. 2013 Nov;67(2):743-51. doi: 10.1007/s12013-013-9564-1.

Güler et al., (2015) [Neurodegenerative changes and apoptosis induced by intrauterine and extrauterine exposure of radiofrequency radiation](#). J Chem Neuroanat. 2015 Oct 28. pii:

Razavinasab M, Moazzami K, Shabani M. (2014). [Maternal mobile phone exposure alters intrinsic electrophysiological properties of CA1 pyramidal neurons in rat offspring](#). Toxicol Ind Health. 30(2), 101-196.

Roggeveen S, van Os J, Viechtbauer W, Lousberg R (2015) [EEG changes due to experimentally induced 3G mobile phone radiation](#). PLoS One. 2015; 10(6): e0129496.

Saikhedkar N, Bhatnagar M, Jain A, Sukhwai P, Sharma C, Jaiswal N. (2014). [Effects of mobile phone radiation \(900 MHz radiofrequency\) on structure and functions of rat brain](#). Neurol Res. 2(6), 2499-2504.

Sirav B, Seyhan N. (2011). [Effects of radiofrequency radiation exposure on blood-brain barrier permeability in male and female rats](#). Electromagnetic Biology and Medicine. 30(4), 253-60.

Sahin et al.,(2016)[The 2100MHz radiofrequency radiation of a 3G-mobile phone and the DNA oxidative damage in brain](#). J Chem Neuroanat. Jan 8.

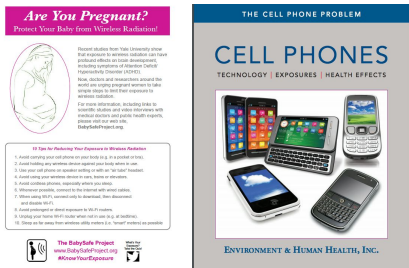
Sonmez OF, Odaci E, Bas O, Kaplan S., (2010) [Purkinje cell number decreases in the adult female rat cerebellum following exposure to 900 MHz electromagnetic field](#). Brain Res. 2010 Oct 14;1356:95-101.

Sudan et al., (2012) [Prenatal and Postnatal Cell Phone Exposures and Headaches in Children](#). Open Pediatr Med Journal. 2012 Dec 5;6(2012):46-52.

Qiao, et al. (2014) [Reduction of Phosphorylated Synapsin I \(Ser-553\) Leads to Spatial Memory Impairment by Attenuating GABA Release after Microwave Exposure in Wistar Rats](#). PLoS ONE. 9(4)

Volkow et al.,(2011). [Effects of cell phone radiofrequency signal exposure on brain glucose metabolism](#). Journal of the American Medical Association, 305(8), 808-13.

Zarei et al., [A Challenging Issue in the Etiology of Speech Problems: The Effect of Maternal Exposure to Electromagnetic Fields on Speech Problems in the Offspring](#). J Biomed Phys Eng. 2015 Sep 1;5(3):151-4. eCollection 2015.



**[The BabySafeProject:](#)** Doctors joining together to educate pregnant women on how to reduce their risk. [Download Poster](#). [Download brochure](#).

**[Cell Phones: Technology, Exposures, Health Effects by Environment and Human Health, Inc.](#)**

Prenatal and Children; Fetal Cell Phone Exposure: How Experimental Studies  
Guide Clinical Practice, Hugh S. Taylor MD. PhD, Chair of Obstetrics,  
Gynecology and Reproductive Sciences, Yale School of Medicine



# Fetal Cell Phone Exposure: How Experimental Studies Guide Clinical Practice

Hugh S. Taylor, M.D.

Chair of Obstetrics, Gynecology and  
Reproductive Sciences

Yale School of Medicine

# Cell Phones

- Use of cell phones has grown dramatically over the last twenty years.
- Operate at frequencies slightly higher than TV and FM Radio signals (Nonionizing).
- Analog and digital phones operate in the frequency range of 900 - 1800 MHz.
- The maximum powers of these phones are 2W and 1W (900 and 1800 MHz respectively). Average power are  $\frac{1}{8}$  of maximum.

# S.A.R.

Specific Energy Absorption Rate  
watts per kilogram

- Electromagnetic waves interacting with matter can be
  - Reflected
  - Absorbed
  - Transmitted
- Exactly what happens depends on
  - the **frequency of the electric field**
  - the **natural frequencies** of the atoms and molecules
- Microwaves emitted by mobile phone systems
  - Are absorbed by human tissue

# Specific energy Absorption Rate (SAR)

watts per kilogram

- Measures energy absorbed per kilogram per second.
- SAR is a property of
  - an emitting device
  - in a particular position with respect to
  - an absorbing substance

## Mobile phones communicate with base stations

- Macrocells - up to about 22 miles. Power output in tens of watts.
- Microcells - infill, airports, railway stations. Range of few hundred yards.
- Picocells - Sited inside buildings. Low power.

# Thermal Effects

- Force produced by an electric field on charged objects (ions in the body) causes them to move, results in electric currents. Currents flowing through resistance of the material results in heating. Heat input causes increased blood flow for heat dissipation (equilibrium).
- Increase in brain temp by cell phones is estimated to be 0.1 C (to equilibrium).

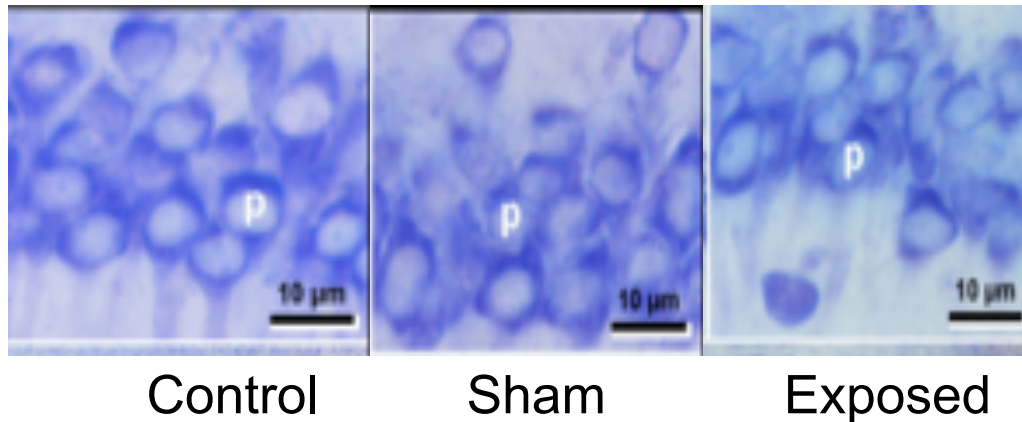
# Plausible Biological Effects of Cell Phone EM Radiation

- Could fields induce cell polarization?
- Alter membrane potential?
- Could fields affect movement of ions through cell membrane channels?
- Does it increase free radical production?
- Do fields effect gene expression?
- Others?
- If any of these effects are real, do they result in an adverse health outcome?

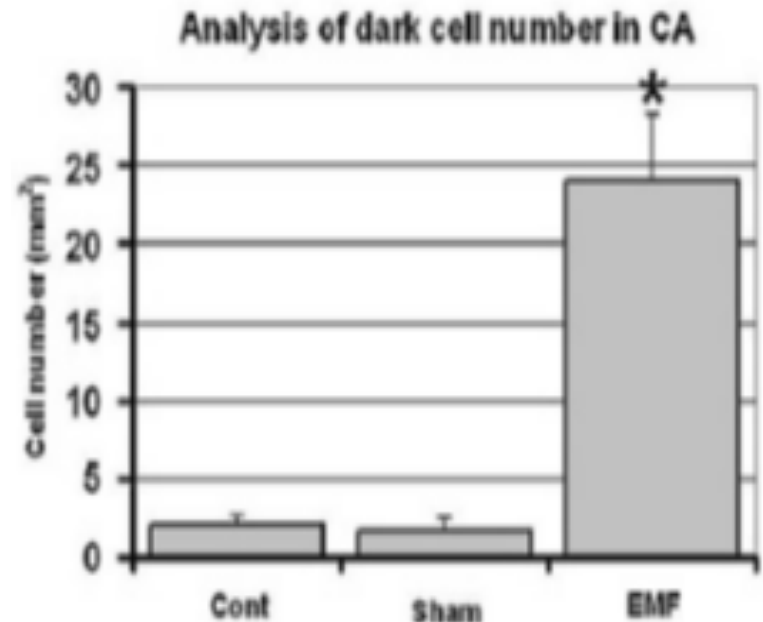


# 900 MHz electromagnetic field exposure affects hippocampal pyramidal cells in adult female rats

1h/day x 28 days; 16 wk females



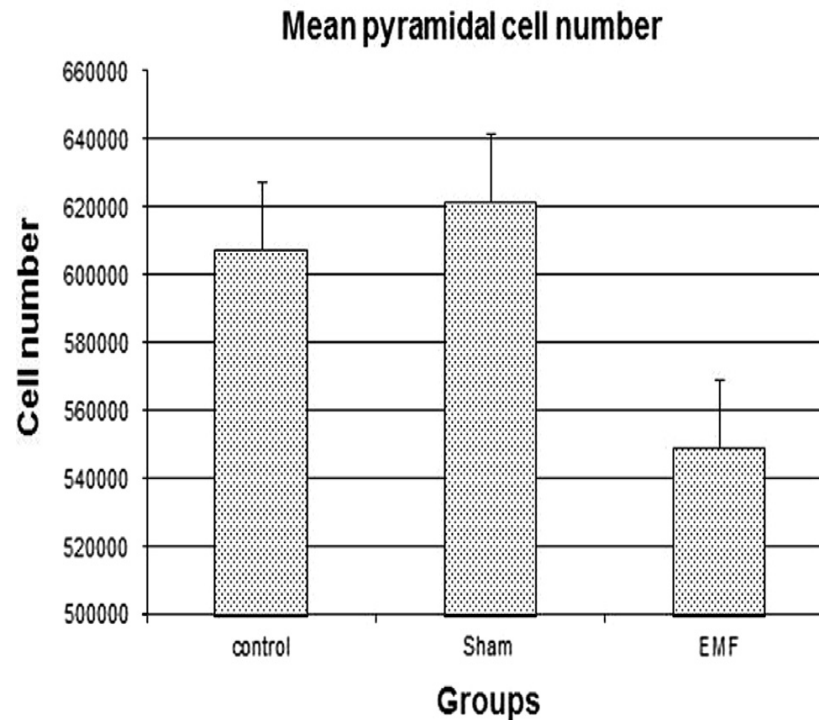
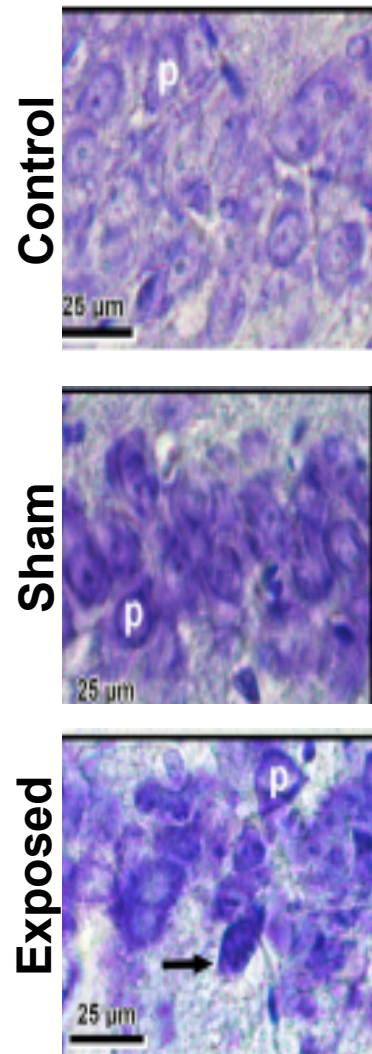
Postnatal EMF exposure caused a significant decrease of pyramidal cells in the Cornu ammonis of the EMF group.



Significantly more dark cells compared with both the control and sham Mean $\pm$ SEM \* $p < 0.01$ .

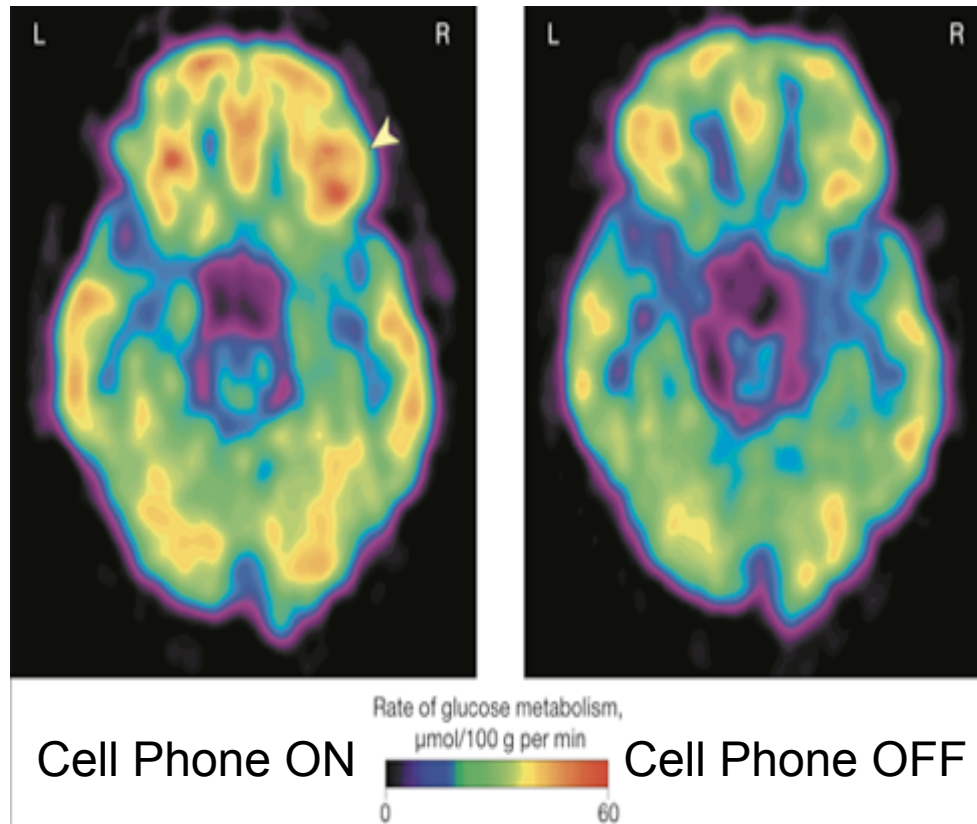
# 900 MHz electromagnetic field exposure affects hippocampal pyramidal cells in prepubescent male rats

Exposure: 1h/day x 30 days; 8 wk males

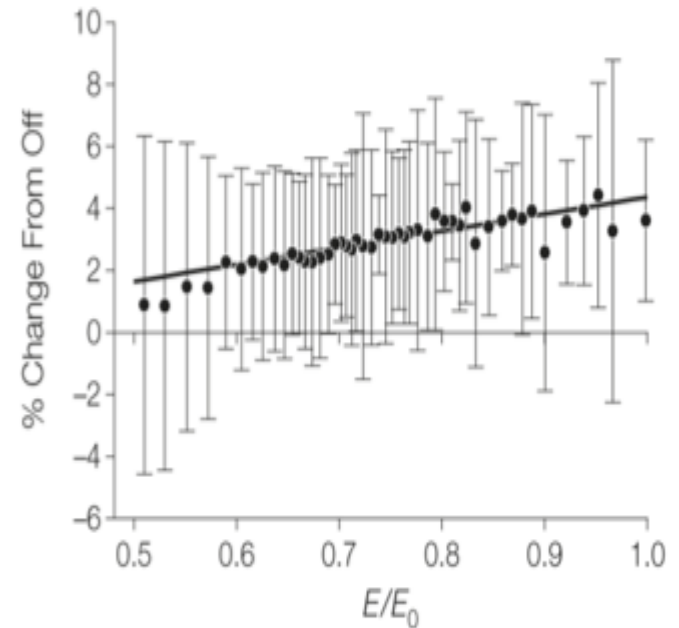


Lower mean number of pyramidal neurons in exposed group than in the control and sham.

# 50 minutes with a cell phone turned on against the ear significantly alters cerebral glucose metabolism



Normalized glucose metabolism higher, at higher brain tissue doses

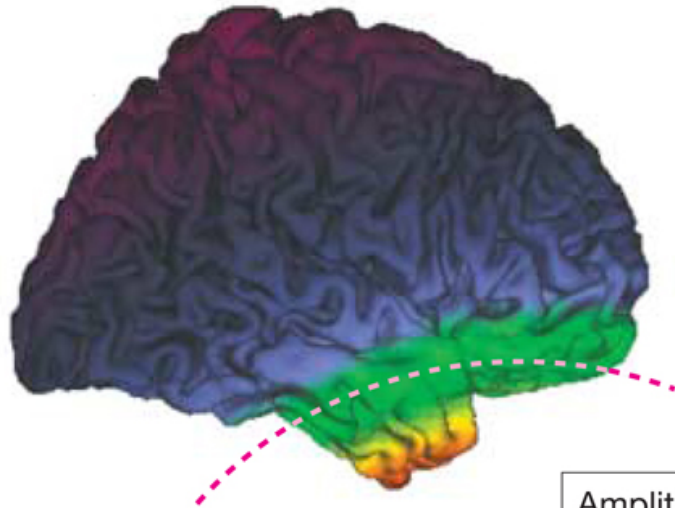


Volkow et al, JAMA, 2011, 305 (8): 808-813.

JA 05529

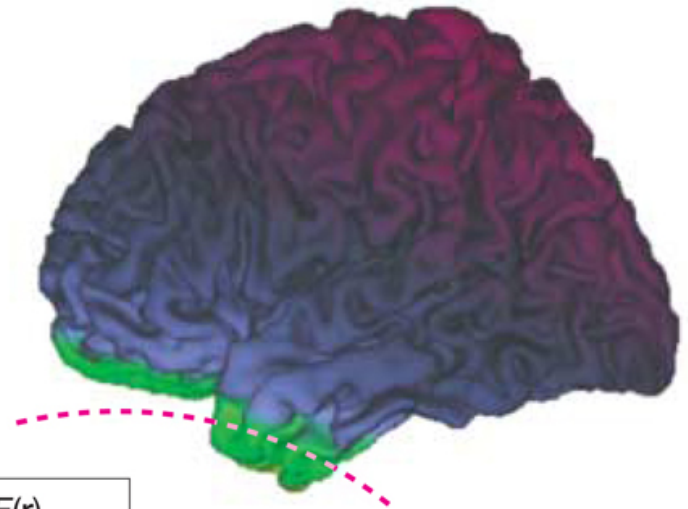
RIGHT HEMISPHERE

Lateral view

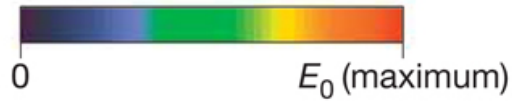


LEFT HEMISPHERE

Lateral view

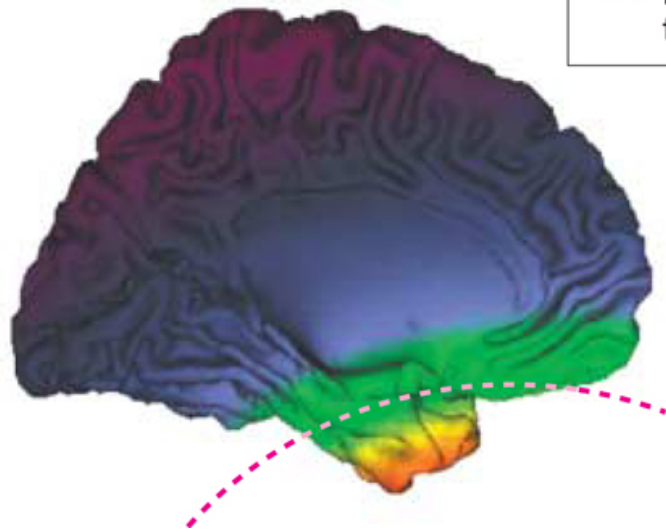


Amplitude of electric field,  $E(r)$

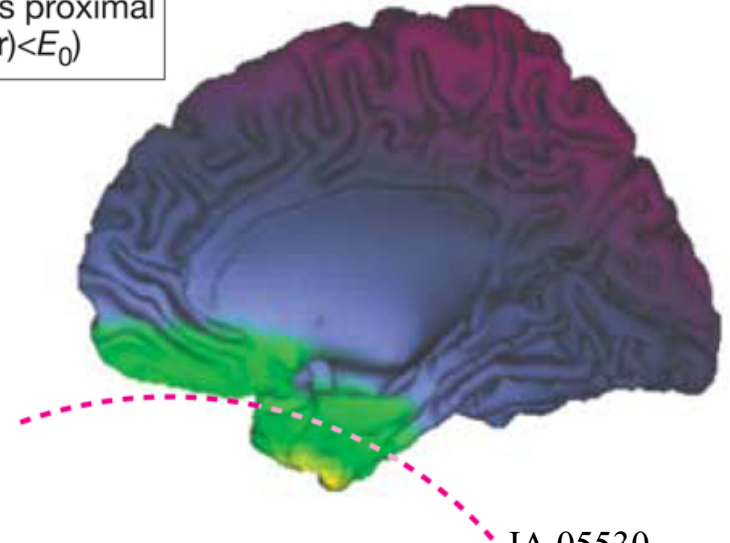


--- Boundary of clusters proximal to antenna ( $E_0/2 < E(r) < E_0$ )

Medial view



Medial view



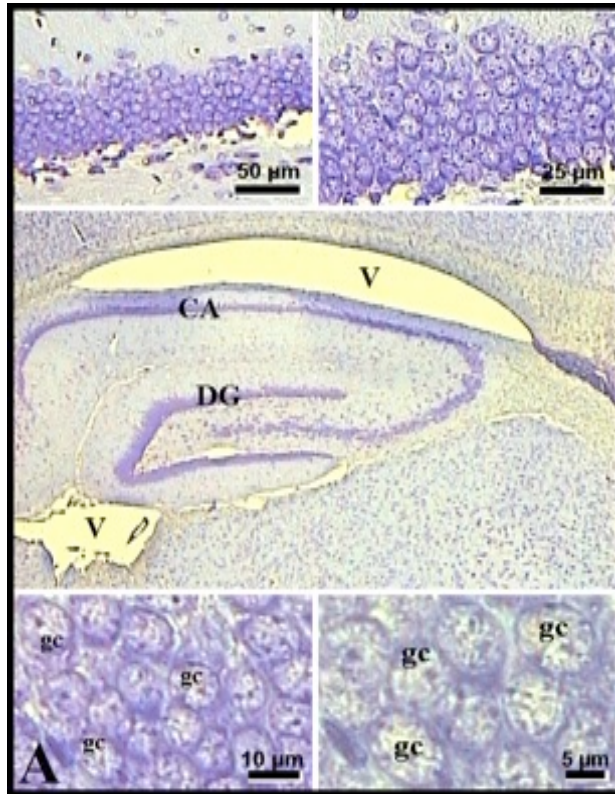


# Cell Phone Use During Pregnancy May be Harmful to the Fetus

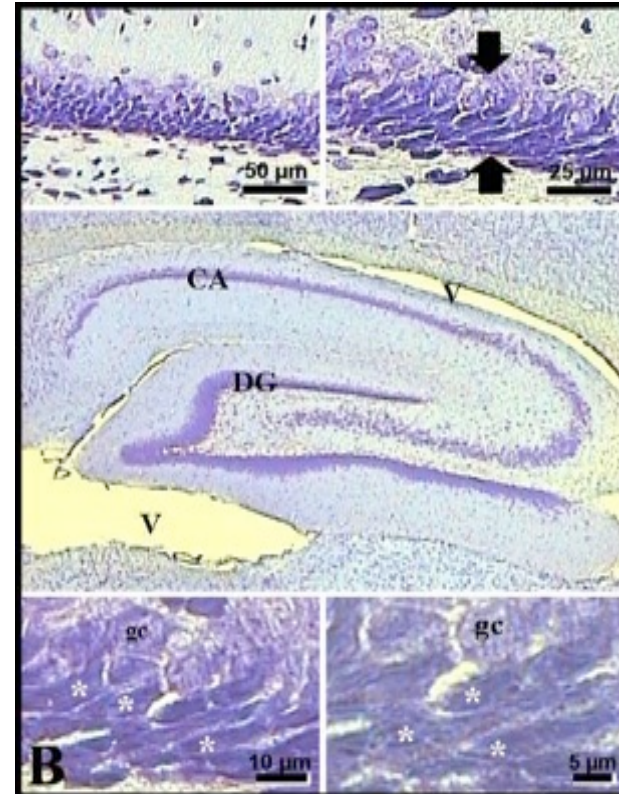


# Fewer, abnormal hippocampal granular cells in the dentate gyrus (DG) of newborn rats following prenatal 900 MHz EMF exposure

**Control**



**Exposed**



Representative photomicrographs and magnifications of the medial region of DG. Control group granular cells normal; most in the EMF group abnormal, condensed. (arrows - dark-blue cells interspersed among normal nerve cells).

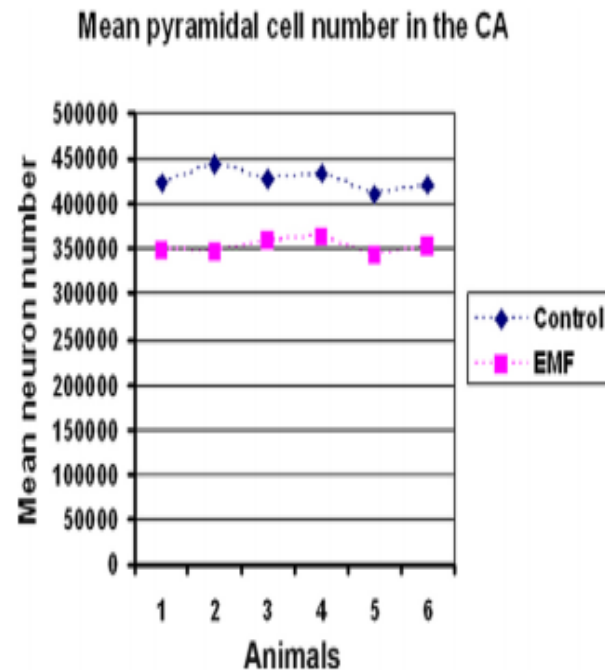
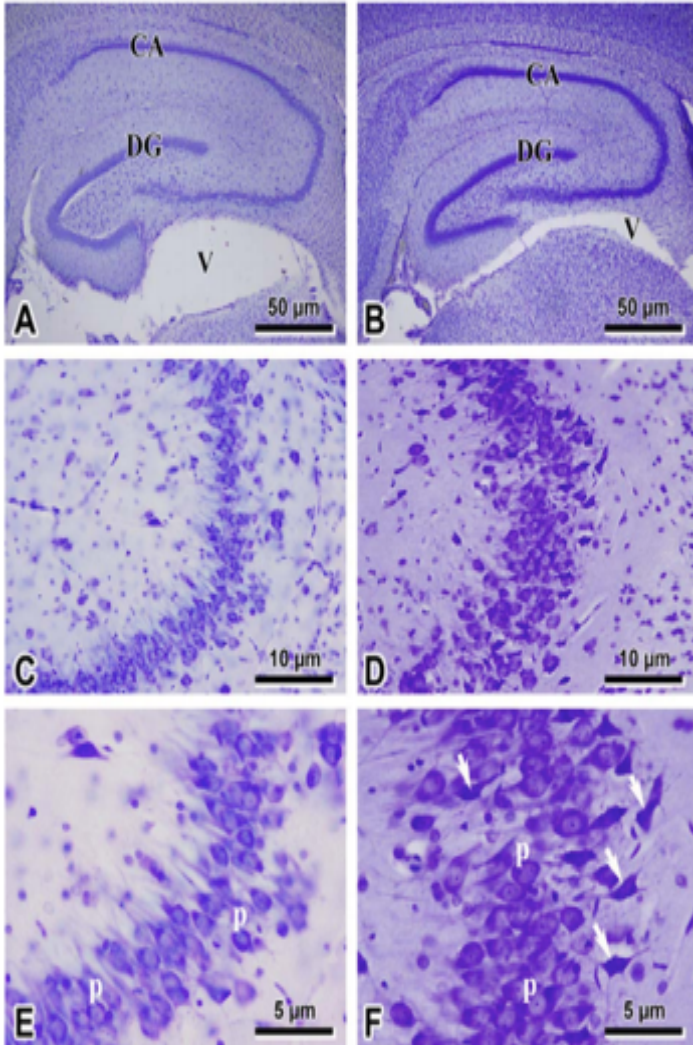


# Fewer pyramidal cells in rat pups' hippocampus with 900 MHz RF prenatal exposure (1h daily x 19 days)

## Control

## Exposed

Hippocampus sections: More cells are abnormal, with shrunken morphology following prenatal EMF exposure.



Significantly fewer pyramidal cells in the cornu ammonis with EMF exposure.



# Prenatal and Postnatal Exposure to Cell Phone Use and Behavioral Problems in Children

- Mothers were recruited to the Danish National Birth Cohort early in pregnancy.
- When the children of those pregnancies reached 7 years of age in 2005 and 2006, mothers were asked to complete a questionnaire regarding the current health and behavioral status of children, as well as past exposure to cell phone use.
- Mothers evaluated the child's behavior problems using the Strength and Difficulties Questionnaire.
- N=13,159

**TABLE 2.** Association of Prenatal and Postnatal Exposure to Cell Phone Use With Overall Behavioral Problems Score

	Postnatal Exposure				Prenatal Exposure <sup>a</sup>	
	No		Yes		Unadjusted OR	Adjusted OR (95% CI) <sup>b</sup>
	Unadjusted OR	Adjusted OR (95% CI) <sup>b</sup>	Unadjusted OR	Adjusted OR (95% CI) <sup>b</sup>		
Prenatal exposure						
No	1.0 <sup>c</sup>	1.0 <sup>c</sup>	1.25	1.18 (0.96–1.45)	1.0 <sup>c</sup>	1.0 <sup>c</sup>
Yes	1.77	1.58 (1.29–1.93)	2.16	1.80 (1.45–2.23)	1.74	1.54 (1.32–1.81)
Postnatal exposure <sup>d</sup>	1.0 <sup>c</sup>	1.0 <sup>c</sup>	1.26	1.18 (1.01–1.38)		

n = 12,068 with information about prenatal and postnatal exposure; n = 12,112 with information about prenatal exposure; n = 13,054 with information about postnatal exposure.

<sup>a</sup>OR for prenatal exposure adjusted for postnatal exposure.

<sup>b</sup>Adjusted for sex of child, age of mother, smoking during pregnancy, mother's psychiatric problems, and socio-occupational levels.

<sup>c</sup>Reference category.

<sup>d</sup>OR for postnatal exposure adjusted for prenatal exposure.

EPIDEMIOLOGY

**TABLE 3.** Associations of Specific Behavioral Problems in Children With Prenatal and Postnatal Exposure to Cell Phone Use

	Prenatal Exposure Only		Postnatal Exposure Only		Both Prenatal and Postnatal Exposure	
	Unadjusted OR	Adjusted OR (95% CI) <sup>a</sup>	Unadjusted OR	Adjusted OR (95% CI) <sup>a</sup>	Unadjusted OR	Adjusted OR (95% CI) <sup>a</sup>
Behavioral problems						
Emotional	1.23	1.12 (0.97–1.30)	1.13	1.06 (0.92–1.23)	1.50	1.25 (1.07–1.47)
Hyperactivity	1.39	1.29 (1.08–1.53)	1.00	0.98 (0.82–1.17)	1.52	1.35 (1.12–1.63)
Conduct problems	1.29	1.21 (1.05–1.40)	1.06	1.02 (0.89–1.18)	1.69	1.49 (1.28–1.74)
Peer problems	1.36	1.27 (1.06–1.52)	1.11	1.08 (0.90–1.29)	1.51	1.34 (1.11–1.63)
Reference category is no prenatal or postnatal exposure to cell phone use.						
<sup>a</sup> Adjusted for sex of child, age of mother, smoking during pregnancy, mother's psychiatric problems, and socio-occupational levels.						

**TABLE 5.** Association of Characteristics of Mother's Cell Phone Use During Pregnancy With Overall Behavioral Problems Score in Children With Prenatal Exposure (n = 3322)

	No. (%)	Unadjusted OR	Adjusted OR (95% CI) <sup>a</sup>	Adjusted OR (95% CI) <sup>a,b</sup>
Times spoken per day				
0–1	1873 (56.4)	1.00 <sup>c</sup>	1.00 <sup>c</sup>	1.00 <sup>c</sup>
2–3	777 (23.4)	1.49	1.33 (0.99–1.79)	1.31 (0.97–1.77)
4+	347 (10.4)	1.60	1.51 (1.02–2.22)	1.47 (1.00–2.18)
Missing	325 (9.8)	—	—	—
<i>P</i> for trend	—	0.28	0.61	0.62
Percentage of time turned on				
0	397 (12.0)	1.00 <sup>c</sup>	1.00 <sup>c</sup>	1.00 <sup>c</sup>
<50	500 (15.1)	0.70	0.62 (0.35–1.11)	0.62 (0.35–1.10)
50–99	954 (28.7)	1.20	0.93 (0.58–1.48)	0.91 (0.57–1.45)
100	1427 (43.0)	1.43	1.09 (0.70–1.70)	1.06 (0.68–1.65)
Missing	44 (1.2)	—	—	—
<i>P</i> for trend	—	0.15	0.13	0.13
<sup>a</sup> Estimates adjusted for sex of child, age of mother, smoking during pregnancy, mother's psychiatric problems, and socio-occupational levels.				
<sup>b</sup> Also adjusted for postnatal exposure to cell phones.				
<sup>c</sup> Reference category.				

EPIDEMIOLOGY

# Conclusions

- Exposure to cell phones prenatally—and, to a lesser degree, postnatally—was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry.
- These associations may be noncausal and may be due to unmeasured confounding. If real, they would be of public health concern given the widespread use of this technology.

# Cell phone use and behavioural problems in young children.

- To see if a larger, separate group of DNBC children would produce similar results after considering additional confounders, children of mothers who might better represent current users of cell phones were analyzed. This 'new' dataset consisted of 28,745 children with completed Age-7 Questionnaires to December 2008.
- The highest OR for behavioral problems were for children who had both prenatal and postnatal exposure to cell phones compared with children not exposed during either time period.
- The adjusted effect estimate was 1.5 (95% CI 1.4 to 1.7).

Controlled study of Fetal  
Radiofrequency  
Radiation Exposure  
From Cellular Telephones  
and Behavior in Adult Mice



# Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz- Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice

Aldad et al, Scientific Reports. 2012; 2: 312.

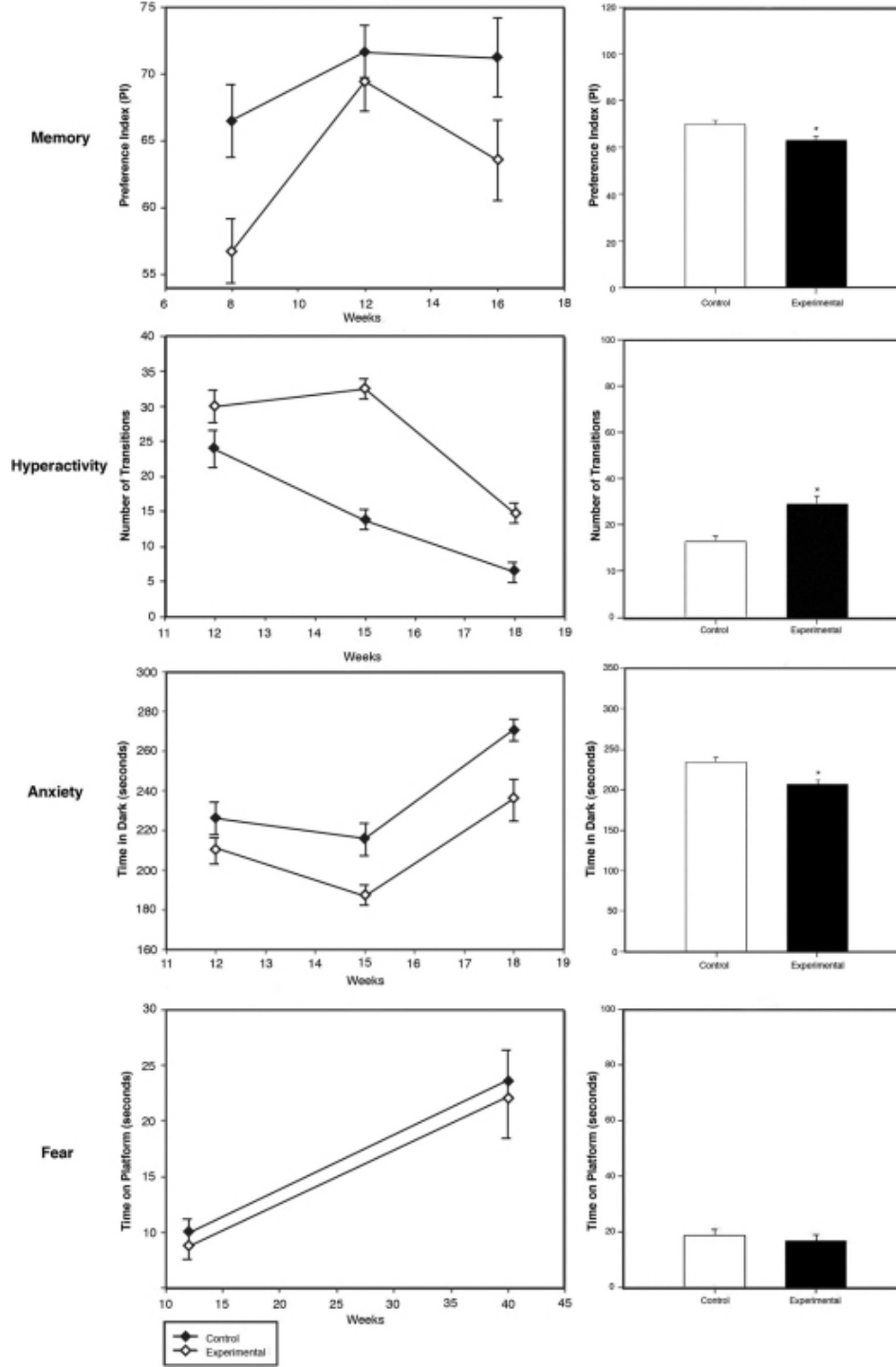
JA 05541

# Fetal Brain Programming

42 pregnant controls



- A muted and silenced 800–1900Mhz cellular phones with a SAR of 1.6W/kg was used.
- The phones were positioned above each cage over the feeding bottle area at a distance of 4.5–22.3cm from each pregnant mouse.
- Mice exposed as a fetus were tested as adults.

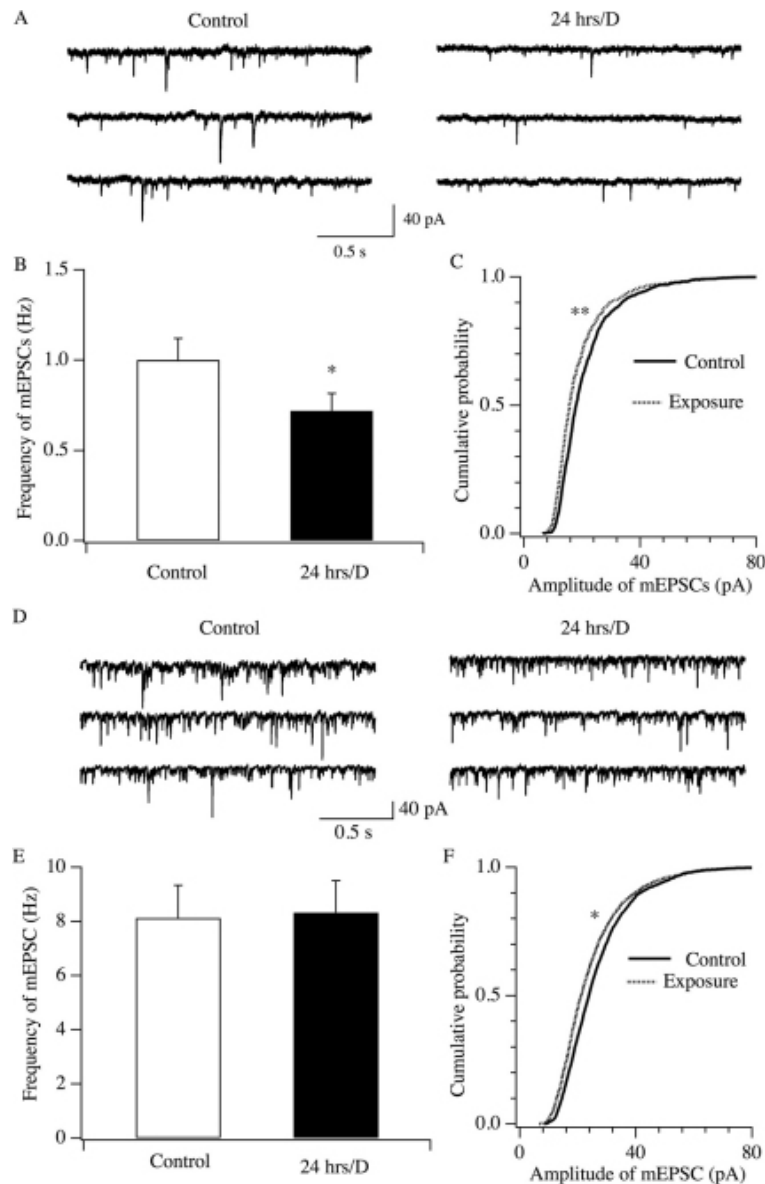


# Definition

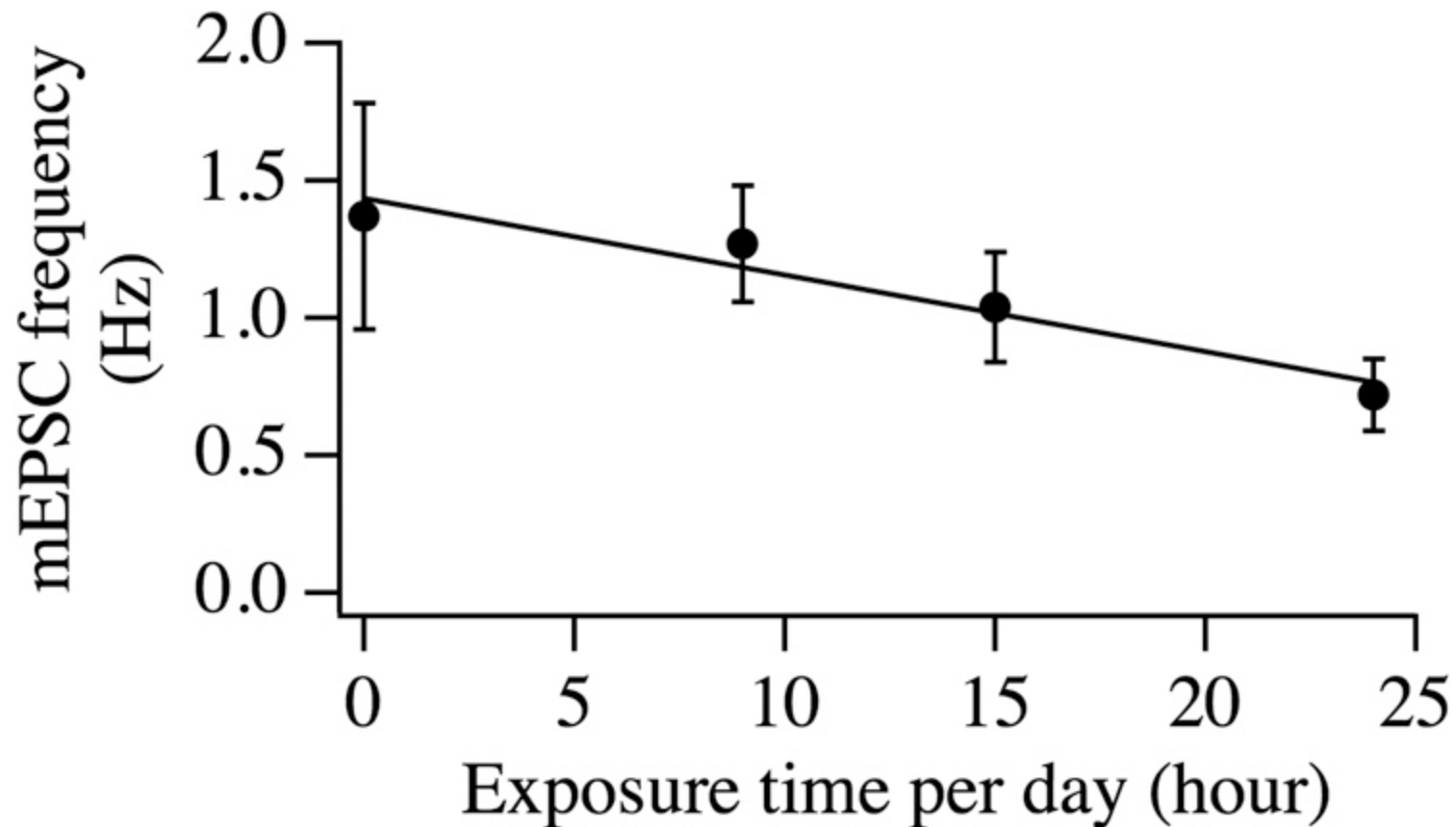
- Attention Deficit Hyperactivity Disorder (ADHD), sometimes called Attention Deficit Disorder (ADD), involves hyperactivity, difficulty paying attention and a tendency to act impulsively.



# Altered Synaptic Efficiency



## Diminished Effect with Decreased Exposure





No brain tumors

No effect of post-natal exposure

# And its not just mobile phones!

- 'WiFi' Wireless Networking
- Bluetooth devices
- Wireless keyboards and mice
- DECT cordless phones
- Baby Monitors
- 'Walkie Talkie'



- All involve electromagnetic waves in the radio and microwave part of the spectrum

# Mobile Phones :

## Comparison of handsets and base stations

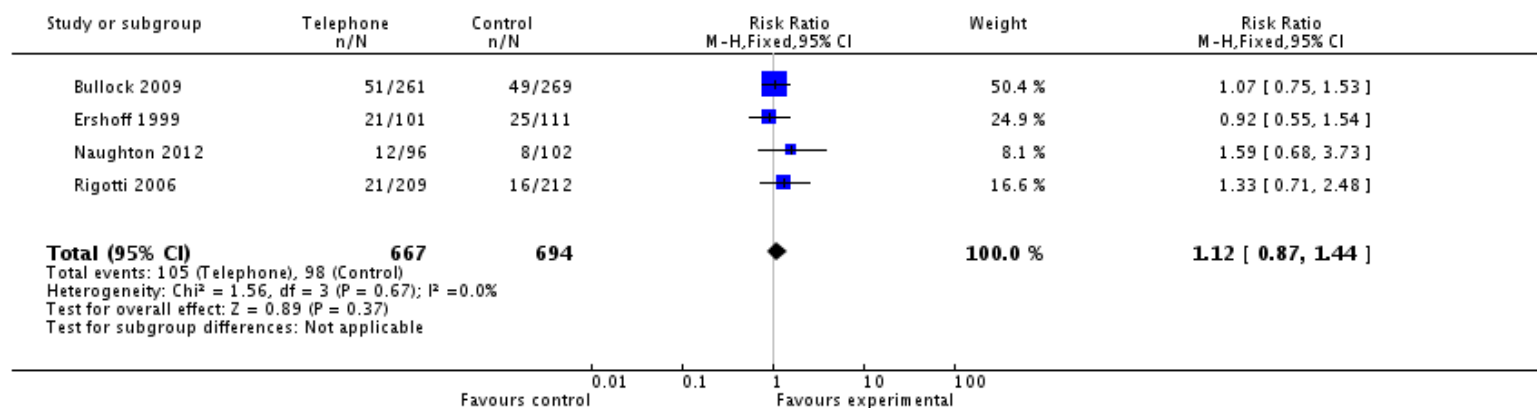
	<b>Power</b>  Watts	<b>Intensity</b>  Watts per square metre	<b>Maximum SAR</b>  Watts per kilogram
<b>Handset</b>	<b>1</b>	<b>200</b>	<b>About 1</b>
<b>Base Station</b>	<b>60</b>	<b>0.01</b>	<b>About 0.001</b>
<b>Wi Fi</b>	<b>0.1</b>	<b>&lt; 0.01</b>	<b>About 0.0001</b>

# **Effectiveness of mHealth [cell phone] interventions for maternal, newborn and child health in low- and middle-income countries.**

Lee et al, J Glob Health. 2016;6(1):010401.

# Telephone support for women during pregnancy and the first six weeks postpartum

Review: Telephone support for women during pregnancy and the first six weeks postpartum  
 Comparison: 1 Telephone support versus any other supportive intervention, or no telephone support  
 Outcome: 18 Positive behaviour change: stopped smoking by the end of pregnancy (cotinine validated)



# Broader Issue:

- What role do the fetal environmental exposures play in the health of the next generation?

Prenatal & Children; Dr. Suleyman Kaplan Comments, Sep. 2, 2013



August 15, 2013

Comment Filed by:

Professor Dr. Suleyman Kaplan,  
Department of Histology and Embryology,  
Kurupelit, Ondokuz Mayıs Üniversitesi,  
55139 Samsun, Turkey

**ET Docket Nos. 03–137 and 13–84; FCC 13–39**

**Background:**

I am currently Editor of the Journal of Experimental and Clinical Medicine, President of the Turkish Society for Stereology, Director of Health Sciences Institute and Head of the Department of Histology and Embryology at Ondokuz Mayıs University, Samsun, Turkey.

I have conducted research in Neurology for over twenty years. I received my M.Sc. in 1987 and my PhD in 1991 from the Dept. of Histology and Embryology, Medical School, Ondokuz Mayıs University, Samsun, Turkey. The title of my PhD thesis was “Neuronal asymmetry in the hippocampus of 4 and 20 weeks old male and female rats.” I have been a Professor since 2000 at the Dept. of Histology and Embryology, Medical School, Ondokuz Mayıs University, Samsun, Turkey. My research and professional experience focuses on Stereology, Obesity, Neurotoxicity, Peripheral nerve regeneration, and Electromagnetic fields (EMF).

I have helped produce four research reports showing that exposure to 900MHz EMF significantly damaged neuronal development in the rat brain. These published studies include:

- Chronic prenatal exposure to the 900 megahertz electrical field induces pyramidal cell loss in the hippocampus of newborn rats (Bas et al., 2009)
- Effects of prenatal exposure to a 900 MHz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study (Odaci, et al., 2008)
- Purkinje cell number decreases in the adult female rat cerebellum following exposure to 900 MHz electromagnetic field (Sonmez et al., 2010)
- 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat (Bas, et al., 2009).

**Summary of Related Research**

**Effects of prenatal exposure to a 900 MHz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study.** Prenatal exposure to 900MHz EMF fields affect nerve cell development in the rat brain. The research report

details how prenatal 900 MHz exposure caused a statistically significant decrease in the number of granule cells in the dentate gyrus of rat offspring. These neurons are an important source of inputs to the hippocampus. The hippocampus is a part of the brain that controls behavior and cognitive functions such as spatial learning and working memory. For this study we used state of the art high precision design based stereological techniques to investigate the impact of 900 MHz exposure on pregnant rat offspring.

We found that exposure caused a progressive postnatal decline in the number of granule cells of dentate gyrus. This suggests that exposure during critical periods of embryonic development damages the normal rat hippocampus development and exposure may also induce neurodevelopment retardation. While animal studies cannot be directly translated to humans, this research would correspond to the third trimester in a human pregnancy. This research showed neural cell loss in the dentate gyrus due to prenatal electromagnetic exposures.

### **Chronic prenatal exposure to the 900-megahertz electrical field induces pyramidal cell loss in the hippocampus of newborn rats.**

Prenatal exposure to 900 MHz decreases pyramidal cells in the hippocampus. This research report details how pregnant rats were exposed to 60 minutes of 900 MHz EMF fields a day for the duration of their pregnancies and later the brains of their offspring were analyzed at four weeks old using the optical fractionator technique. The exposed offspring showed a significant reduction in the total number of pyramidal cells.

The pyramidal cells are located in the cornu ammonis of the hippocampus, which involves short-term memory and learning. This research suggests that electromagnetic fields could disturb the development of the cornu ammonis, which could result in impaired short-term memory and learning.

### **900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat.**

900 MHz EMF exposure induces neuronal damage and cell loss in the rat hippocampus. The report documents our research exposing female rats to 900 MHz from 12 weeks to 16 weeks of age.

Stereological analyses using the optical fractionator technique were done blind to obtain unbiased results. The results showed a statistically significant decrease in the pyramidal cells of the hippocampus and also showed an increase in dark cells. This research again shows impacts on the part of the brain involved in memory and learning. Sixteen-week-old rats are comparable to the age of human teenagers.

### **Purkinje cell number decreases in the adult female rat cerebellum following**

**exposure to 900 MHz electromagnetic field.** 900 MHz EMF effects neuron number in the cerebellum. The cerebellum is a region of the brain that is thought to be involved in cognitive functions such as attention and language (and in regulating fear and pleasure responses) in addition to it's role in motor control (coordination, precision and equilibrium). This research report documents our research on the effect of 900 MHz EMF on the number of Purkinje cells in the adult female rat cerebellum. Purkinje cells are important neurons in the cerebellum. In this study we exposed rats to 900MHz for one hour a day from 12 to 16 weeks of age and blind analyzed their Purkinje cells with the

optical fractionator technique. Results showed the exposed rats had significantly lower total numbers of Purkinje cells in their cerebellum. This suggests that long-term exposures to 900 MHz EMF leads to decreases of Purkinje cell numbers in the female rat cerebellum. Sixteen-week-old rats correspond to human teenagers for developmental stage comparison.

**900 MHz EMF exposures at a SAR of 2W/Kg seem to have significant non-thermal biological effects.** In the two research studies of 900 MHz exposures to the adult rat brain the specific energy absorption rate (SAR) varied between 0.016 (whole body) and 2W/kg (locally in the head). In the two research studies on prenatal exposure a 900 MHz continuous wave electromagnetic energy generator SAR of 2W/kg was used on the pregnant mice.

This research provides useful data on the possible toxic effects of EMF exposure on the Central Nervous System during critical periods of brain development. We conducted our research with 900 MHz EMF based on the fact that so many mobile phones operate at this frequency. In our research, the body weight of the rats did not show any effects from exposure, so there was no outward visual abnormality. However, the significant negative impact on neuron production in the hippocampus and cerebellum raises serious questions about the possible non thermal effects of electromagnetic fields on the parts of the mammal brain that involve attention, learning and memory.

**The non-thermal biological effects of EMF exposure are of increasing concern to scientists.** The research our lab has done fits into a larger context of research showing electromagnetic fields have adverse effects on animal tissue. (Dutta et al., 1989; Odaci et al., 2008; Bas et al., 2009a,b; Ragbetli et al., 2010, 2009; Ammani et al., 2010; Maskey et al., 2010). Several studies indicate that EMFs emitted by mobile phones could affect body tissue, systems and their physiologic activities (Mausset et al., 2001; Mausset-Bonnefont et al., 2004; Salford et al., 2003; Koyu et al., 2005; Yildiz et al., 2006; Manikonda et al., 2007).

\* \* \*

### **Specific Comments on the FCC's Notice of Inquiry**

In its Notice of Inquiry the FCC asks: “..whether its current limits are appropriate as they relate to device use by children.” (p.2, Item 53).

The answer is a No. Current limits may not be appropriate as they relate to device use by children due to their vulnerability and developing bodies. Over the past few decades, several experimental studies have emerged which indicate electromagnetic fields could affect brain activity and neurons at the cellular level. The research from our laboratory shows that chronic exposure to electromagnetic fields can have long-term effects in brain morphology. The use of mobile phones by children and teenagers deserves special concern because this group will experience much higher cumulative exposure to EMF than previous generations.

Research on the mammal brain such as I have documented in this submission raises the question as to whether children and the developing fetus are more sensitive to EMF exposure than adults. The brain is particularly vulnerable during the growth process, which begins at conception and continues through the teen years. The research I have documented in rats corresponds to EMF exposure during the human developmental stages of the embryo and the teen years. Neuron production begins during gestation, through the early postnatal period and then continues at a slower rate into adulthood. Environmental insults during the early growth stages can have profound impacts later in life. While animal studies cannot be directly translated to humans, similar effects in humans would have far reaching consequences for future generations.

B. On p.4, Item 63 of the Inquiry the Commission requests comment on "*whether the Commission should consistently require either disclosure of the maximum SAR value or other more reliable exposure data in a standard format, perhaps in manuals, at point-of-sale, or on a Web site.*"

Again, the answer is YES. Consumers should know the details of exposures that are possible from the phone or device they buy. Consumers should be provided with this information in order to make informed decisions.

In the introduction to FCC 13-39 Section 5 Inquiry, the FCC asks, "*whether our exposure limits remain appropriate given the differences in the various recommendations that have developed and recognizing additional progress in research subsequent to the adoption of our existing exposure limits.*"

The answer is NO. Recent research is raising questions as to the appropriateness of the current exposure limits. The research I have presented shows significant non-thermal biological health impacts from lower intensity electromagnetic fields. While further research is critical to fully understand the possible effects on brain development, this research adds to accumulating evidence that the current exposure levels may not protect from non-thermal biological health effects. Exposure limits should protect humans from adverse biological effects.

Respectfully submitted,

Dr. Suleyman Kaplan

---

**Citations:** Ammari, M., Gamez, C., Lecomte, A., Sakly, M., Abdelmelek, H., De Seze, R., 2010. GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field signal. *Int. J. Radiation Biol.* 86, 367–375.

- Bas, O., Odaci, E., Mollaoglu, H., Ucok, K., Kaplan, S., 2009a. Chronic prenatal exposure to the 900 megahertz electromagnetic field induces pyramidal cell loss in the hippocampus of newborn rats. *Toxicol. Ind. Health* 25, 377–384.
- Bas, O., Odaci, E., Kaplan, S., Acer, N., 2009b. 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in adult rat. *Brain Res.* 1265, 178–185.
- Dutta, S.K., Ghosh, B., Blackman, C.F., 1989. Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture. *Bioelectromagnetics* 10, 197–202.
- Koyu, A., Cesur, G., Ozguner, F., Akdogan, M., Mollaoglu, H., Ozen, S., 2005. Effects of 900 MHz electromagnetic field on TSH and thyroid hormones in rats. *Toxicol. Lett.* 157, 257–262.
- Ragbetli, M.C., Aydinlioglu, A., Koyun, N., Ragbetli, C., Bektas, S., Ozdemir, S., 2010. The effect of mobile phone on the number of Purkinje cells: a stereological study. *Int. J. Radiation Biol.* 86, 548–554.
- Ragbetli, M.C., Aydinlioglu, A., Koyun, N., Ragbetli, C., Karayel, M., 2009. Effect of prenatal exposure to mobile phone on pyramidal cell numbers in the mouse hippocampus: a stereological study. *Int. J. Neurosci.* 119, 1031–1041.
- Manikonda, P.K., Rajendra, P., Devendranath, D., Gunasekaran, B., Channakeshava, Aradhya, R.S., Sashidhar, R.B., Subramanyam, C., 2007. Influence of extremely low frequency magnetic fields on Ca<sup>2+</sup> signaling and NMDA receptor functions in rat hippocampus. *Neurosci. Lett.* 413, 145–149.
- Maskey, D., Kim, M., Aryal, B., Pradhan, J., Choi, I.Y., Park, K.S., Son, T., Hong, S.Y., Kim, S.B., Kim, H.G., Kim, M.J., 2010. Effect of 835 MHz radiofrequency radiation exposure on calcium binding proteins in the hippocampus of the mouse brain. *Brain Res.* 1313, 232–241.
- Mausset, A.L., de Seze, R., Montpeyroux, F., Privat, A., 2001. Effects of radiofrequency exposure on the GABAergic system in the rat cerebellum: clues from semiquantitative immunohistochemistry. *Brain Res.* 912, 33–46.
- Mausset-Bonnefont, A.L., Hirbec, H., Bonnefont, X., Privat, A., Vignon, J., de Seze, R., 2004. Acute exposure to GSM 900-MHz electromagnetic fields induces glial reactivity and biochemical modifications in the rat brain. *Neurobiol. Dis.* 17, 445–454.
- Odaci, E., Bas, O., Kaplan, S., 2008. Effects of prenatal exposure to a 900 megahertz electromagnetic field on the dentate gyrus of rats: a stereological and histopathological study. *Brain Res.* 1238, 224–229.
- Odaci, E., Cihan, O.F., Aslan, H., Ragbetli, M.C., Kaplan, S., 2010. Prenatal diclofenac sodium administration increases the number of Purkinje cells in female rats: a stereological study. *Int. J. Dev. Neurosci.* 28, 145–151.
- Salford, L.G., Brun, A.E., Eberhardt, J.L., Malmgren, L., Persson, B.R., 2003. Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones. *Environ. Health Perspect.* 111, 881–883.
- Sonmez OF, Odaci E, Bas O, Kaplan S., 2010. Purkinje cell number decreases in the adult female rat cerebellum following exposure to 900 MHz electromagnetic field. *Brain Res.* 2010 Oct 14;1356:95-101.
- Yildiz, M., Cicek, E., Cerci, S.S., Cerci, C., Oral, B., Koyu, A., 2006. Influence of electromagnetic fields and protective effect of CAPE on bone mineral density in rats. *Arch. Med. Res.* 37, 818–821.

Prenatal & Children; Amended Declaration of Dr. David O. Carpenter M.D.  
(Dec. 20, 2011); Morrison et al v. Portland Schools, No. 3:11-cv-00739-MO  
(U.S.D.C. Oregon, Portland Div.)

**Shawn E. Abrell**, WSB No. 41054, *Pro Hac Vice*  
4614 SW Kelly Avenue, Suite 200, Portland, Oregon 97239  
Tel.: 971.258.0333; Fax: 503.222.0693  
E-Mail: shawn.e.abrell@gmail.com  
*Lead Counsel for Plaintiffs*

**Tyl W. Bakker**, OSB No. 90200  
621 SW Alder, Suite 621, Portland, Oregon 97205  
Tel.: 503.244.4157; Fax: 503.220.1913  
E-Mail: tylbakker@gmail.com  
*Local Counsel for Plaintiffs*

**United States District Court**

**District of Oregon**

**Portland Division**

**AHM**, by and through  
her Guardian *ad litem* and father,  
David Mark Morrison, and  
**David Mark Morrison**, individually,

v.

**Portland Public Schools,**

Defendant.

Civil Action No. 3:11-cv-00739-MO

**Amended Declaration of  
Dr. David O. Carpenter, M.D.**

I, Dr. David O. Carpenter, M.D., under penalty of perjury pursuant to 28 U.S.C. § 1746,  
hereby make the following declaration in support of an injunction against Portland Public Schools'  
use of WI-FI:



1. I am a public health physician, educated at Harvard Medical School. My current title is Director of the Institute for Health and the Environment at the University at Albany and Professor of Environmental Health Sciences within the School of Public Health. Formerly, I was the Dean of the School of Public Health at the University of Albany and the Director of the Wadsworth Center for Laboratories and Research of the New York State Department of Health.

2. I served as the Executive Secretary to the New York State Powerlines Project in the 1980s, a program of research that showed children living in homes with elevated magnetic fields coming from powerlines suffered from an elevated risk of developing leukemia. After this I became the spokesperson on electromagnetic field (EMF) issues for the state during the time of my employment in the Department of Health. I have published several reviews on the subject and have edited two books.

3. I am a Co-Editor and a Contributing Author of the *BioInitiative: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, [www.bioinitiative.org](http://www.bioinitiative.org). It documents bioeffects, adverse health effects and public health conclusions about impacts of electromagnetic radiation (electromagnetic fields including extremely-low frequency ELF-EMF and radiofrequency /microwave or RF-EMF fields). The public health chapter from this report was subsequently published in a peer-reviewed journal.

4. Additionally, I am a Co-Author of *Setting Prudent Public Health Policy for Electromagnetic Field Exposures*, *Reviews on Environmental Health*, Volume 23, No 2, 2008, attached as Addendum A-2.

5. In addition, in 2009, I was invited to present to the President's Cancer Panel on the subject of powerline and radiofrequency fields and cancer, and have testified on this issue before the United States House of Representatives.

6. In sum, I am a public health physician, professor and former public health school Dean with expertise in electrophysiology, low-frequency electromagnetic fields bioeffects, and

radiofrequency (RF) and microwave (MW) radiation bioeffects.

7. WI-FI deploys pulse-modulated (“PM”) microwave (“MW”) radiation (within the larger RF radiation spectrum) with a carrier frequency that is similar to that used by a microwave oven: about 2.45 GHz. This is the “Agent”. The 2.45 GHz frequency was chosen for the oven because of its wavelength and harmonic resonance with the water molecule, to ensure the most efficient absorption by living tissues and effective heating by way of the agitation of water at the molecular level. The pulse-modulation of a wave with lower frequencies in addition to the high-frequency carrier signal, increases the exposure complexity and in turn the bioeffects in an exposed population.

8. In the context of school development, WI-FI exposes building occupants including children and adults constantly from both computers and infrastructure antennas. Duration may be an even more potent contributing factor to RF/MW radiation bioeffects than exposure levels. Chronic, such as all-day, school exposure, is more likely than short and intermittent exposure, such as cell phone use, to produce harmful health effects, and is likely to do so at lower exposure levels.

9. Persons stationed close to school computers with WI-FI and especially those very near to any WI-FI infrastructure will receive considerably higher exposure than do others.

10. It is generally accepted within the relevant scientific community and has been established beyond any reasonable doubt that adverse human health effects occur at far lower levels of RF/MW radiation exposure than those that cause noticeable heating, particularly where the wavelength approaches body-part size and thus maximizes absorption, where the wavelength has resonance with the water molecule, where there is more complex, modulated wave, where there is chronic exposure duration, and where exposed persons lack the capacity voluntarily to remove themselves from radiation sources.

11. Some effects are shown to occur at several hundred thousand times below the FCC public exposure guidelines, which are set based on the fallacious assumption that there are no adverse health effects at exposures that do not cause easily measureable heating. FCC guidelines

also only apply to 30-minute public exposures; therefore do not even infer safety at durations >30 minutes, such as in a school setting.

12. Exposure to high-frequency RF and MW radiation and also the extreme low frequency (ELF) EM fields that accompany WI-FI exposure have been linked to a variety of adverse health outcomes. Some of the many adverse effects reported to be associated with and/or caused by ELF fields and/or RF/MW radiation include neurologic, endocrine, immune, cardiac, reproductive and other effects, including cancers.

13. Studies of isolated cells have shown that RF/MW exposures may cause changes in cell membrane function, cell communication, metabolism, activation of proto-oncogenes, and can trigger the production of stress proteins at exposure levels below FCC guidelines and also at and less than school WI-FI exposure levels and parameters. Resulting effects in cellular studies include without limitation DNA breaks and chromosome aberrations, cell death including death of brain neurons, increased free radical production, activation of the endogenous opioid system, cell stress and premature aging.

14. Human studies of comparable RF/MW radiation parameters show changes in brain function including memory loss, retarded learning, performance impairment in children, headaches and neurodegenerative conditions, melatonin suppression and sleep disorders, fatigue, hormonal imbalances, immune dysregulation such as allergic and inflammatory responses, cardiac and blood pressure problems, genotoxic effects like miscarriage, cancers such as childhood leukemia, childhood and adult brain tumors, and more.

15. There is consistent evidence for increased incidence of effects in individuals who live near to high-power short-wave, AM, FM and TV transmission towers. This is particularly relevant because, like WI-FI, radio-TV transmission towers give continuous, whole-body radiation, not just radiation to the head, constantly.

16. Since WI-FI transmitters, both infrastructural and on computers, are indoors, where children and teachers may be very close by, and since WI-FI, at 2.45 GHz, deploys a

wavelength, at ~12.2 cm or ~ 4.8 inches, more absorbable by children's and adults' bodies and brains than radio-TV wavelengths, the harmfulness of WI-FI radiation likely exceeds that of radio-TV towers.

17. Like second-hand smoke, EMF and RF/MW radiation involve complex mixtures, where different frequencies, intensities, durations of exposure(s), modulation, waveform and other factors are known to produce variable effects, often more harmful with greater complexity. Decades of scientific study have produced substantial evidence that EMF and RF/MW radiation may be considered neurotoxic, carcinogenic and genotoxic. Sources of fields and radiation, but are not limited to: power lines, navigational radar, cell phones, cordless phones [or Digitally Encoded Cordless Transmission Devices (D.E.C.T.) phones], cell towers, 'smart' meters and their grids or infrastructure, "smart" boards, meters and grids, WiMax and wireless internet (WI-FI).

18. The RF/MW radiation and low-frequency EMF science that currently exists includes tens of thousands of studies dating back to the 1920s. On the basis of this vast body of literature, many public health experts believe, myself included, that it is likely society will face epidemics of neurotoxic effects and degeneration, cancers and genotoxicity in the future, resulting from the extreme and mostly involuntary exposure to RF/MW radiation and EMFs. WI-FI radiation in schools exceeds natural background levels of microwave radiation by trillions of times. Thus, it is important that all of us restrict our use of cell phones, and be as free as possible from exposure to unnatural, background sources of MW radiation, particularly WI-FI.

19. In public health science, it is generally accepted fact that vulnerable subgroups exist within any human population. This is also recognized specifically for RF/MW radiation and fields. These groups include children, pregnant women, the elderly and those with preexisting illnesses and/or impairments. Children are more vulnerable to RF/MW radiation because of the susceptibility of their developing nervous systems. RF/MW penetration is greater relative to head size in children, who have a greater absorption of RF/MW energy in the tissues of the head at WI-FI frequencies.

Such greater absorption results because children's skulls are thinner, their brains smaller, and their brain tissue is more conductive than those of adults, and since it has a higher water content and ion concentrations. The Presidential Cancer Panel found that children 'are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation.'

[http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP\\_Report\\_08-09\\_508.pdf](http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf)

20. FCC public RF/MW radiation exposure guidelines are based on the height, weight and stature of a 6-foot tall man, not children or adults of smaller stature. The guidelines do not take into account the unique susceptibility of growing children to exposures. Since children are growing, their rate of cellular activity and division is more rapid, and they are at more risk for DNA damage and subsequent cancers. Growth and development of the central nervous system is still occurring well into the teenage years, such that the neurological impairments predictable by the extant science may have great impact upon development, cognition, learning, and behavior. Prenatal exposure has been identified as a risk factor for childhood leukemia, and is associated with miscarriage. Children are largely unable to remove themselves from exposures to harmful substances in their environments. Their exposure is involuntary.

21. When WI-FI is in operation in a school, children and their parents have no choice but to allow the school to expose them to trillions of times higher microwave radiation than exists naturally on Earth at the same frequencies. Children and other building users are exposed to as much as 30-40 hours per week of constant, digitally encoded WI-FI signals from each wireless device and infrastructural antenna in a school building. Based upon a review of the Mount Tabor WI-FI Floor Plan, a given child is subject to direct signals from multiple WI-FI transmitters, including rooms full of students and teachers transmitting numerous laptop and other wireless signals. There is a major legal difference between an exposure that an individual chooses to accept and one that is forced upon a person, especially a dependent, who can do nothing about it.

22. WI-FI in the Portland Schools deploys similar PM MW radiation, at 2.45 and 5 GHz, to that of cell and cordless phones and their infrastructure. There is clear and strong evidence that intensive use of cell phones increases incidence of brain cancer, tumors of the auditory nerve, and cancer of the parotid gland, the salivary gland in the cheek by the ear. Cell and cordless phone radiation closely resembles that of WI-FI radiation exposure, except that WI-FI is more hazardous by way of frequency, duration, and the involuntary nature of exposure. While a cell or cordless phone is used only intermittently and primarily voluntarily, a WI-FI radiation microenvironment is constant in duration, with unavoidable radiation exposure even when nearby students are not actively using it. Because WI-FI radiation is essentially the same as, but more hazardous than, that for cell and cordless phones, there is every reason to understand that the health effects will be the same or worse, varying in relation to the total dose of radiation, and intensified by the constancy of duration. There is evidence from Scandinavian studies of cell phone usage that children who use cell phones are about five times more likely to develop brain cancer than if their usage starts as an adult. Thus, it is especially necessary to protect children from pulse-modulated MW radiation such as both cell phones and WI-FI deploy.

23. Based on a high degree of scientific certainty, Portland Public Schools' use of WI-FI is causing and will continue to cause AHM, other students, and school staff and faculty adverse health effects, and should be discontinued immediately. Educating by way of the Internet via cabled systems only decreases MW radiation exposure and is of minimal expense.

24. Having reviewed hundreds, possibly thousands, of studies in RF/MW radiation and ELF fields, published from decades ago to the present, I would provide you the following primary evidence, without limitation. Due to the active suppression of the RF/MW literature, some researchers in public health science are less aware of these studies. However, the forefront experts specializing in these areas, RF/MW radiation and ELF fields, recognize the certainties in this large body of scientific literature, which establishes without limitation that PM MW radiation with chronic duration is quite harmful to humans, particularly children, as well as to animals and plants.

25. It is not surprising that even as of 1990, the US Environmental Protection Agency ("EPA") had determined RF/MW radiation a "probable carcinogen". Now that we have much more confirming study in the interim, the conclusion is yet more certain. And when we focus on MW radiation, particularly pulse-modulated radiation, on long, non-intermittent duration and on more vulnerable subgroups such as children, we see that the cancer outcome is very certain, indeed. Amongst the epidemiologic studies showing cancer outcomes, the following are particularly strong:

- a. Dode AC, Leao M, Tejo FdeAF, gomes ACR, Dode DC, Dode MC, Moreira CW, Condessa VA, Albinatti C and Calaffa WT. Mortality by neoplasia and cellular telephone base stations in the Belo Horizonte municipality, Minas Gerais State, Brazil. *Sci Total Environ* 409: 3649-3665:2011. This study shows higher rates of cancer in people living close to cell phone towers than for people living further away. Cell phone radiation is similar to but likely not as harmful as 2.45 GHz radiation from WI-FI. The exposure levels in this study are lower than those that Portland school building occupants receive from WI-FI.
- b. Oberfeld G. Environmental Epidemiology Study of Cancer Incidence in the Municipalities of Hausmannstatten & Vasoldsberg (Austria), 2008. This government-commissioned study found significantly increased cancer risk relative to a lower-exposure reference category, 23x higher for breast cancer and 121x higher for brain tumors, with strong exposure-effect relations.
- c. Michelozzi P, Capon A, Kirchmayer U, Forastiere F, Biggeri A, Barca A and Perucci CA. Adult and childhood leukemia near a high-power radiostation in Rome, Italy. *Am J Epidemiol.* 155: 1098-1103: 2002. The authors show that there is a significant elevation of childhood leukemia among residents living near to Vatican Radio, and that the risk declines with distance away from the transmitter. This is RF radiation in frequencies similar to that of WI-FI.

- d. Ha M, Im H, Lee M, Kim HJ, Kim BC, Gimm YM and Pack JK. Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. *Am J Epidemiol* 166: 270-279: 2007. Leukemia and brain cancer in children in Korea were investigated in relation to residence within 2 km of AM radio transmitters. There was a significant elevation in rates of leukemia but not of brain cancer. WI-FI radiation is more harmful than AM.
- e. Park SK, Ha M, Im HJ. Ecological study on residences in the vicinity of AM radio broadcasting towers and cancer death: preliminary observations in Korea. *Int Arch Occup Environ Health*. 2004 Aug;77(6):387-94. This study found higher mortality areas for all cancers and leukemia in some age groups in the area near the AM towers.
- f. Hallberg O. Johansson O. *Med Sci Monit* 2004 Jul;10(7):CR336-40. Malignant melanoma of the skin – not a sunshine story! Increased incidence and mortality from skin melanoma are concluded to result from continuous disturbances of cell repair mechanisms by body-resonant EMFs from FM/TV networks.
- g. Hallberg O. Johansson O. 2005. FM Broadcasting exposure time and malignant melanoma incidence, *Electromagnetic Biology and Medicine* 24;1-8. Age-specific incidence of malignant melanoma of the skin is related to FM broadcasting radiation at whole-body resonant frequencies. This is very relevant to children, since the smaller wavelengths of WI-FI are at resonant frequencies with dimensions of the human head, particularly the child's head.
- h. Dolk H, Shaddick G, Walls P, Grundy C, Thakrar B, Kleinschmidt I, Elliot P. Cancer Incidence near radio and television transmitters in Great Britain. I – Sutton-Colfield transmitter, and II. Al high-power transmitters. *Am J Epidemiol* 1997; 145(1):1-9 and 10-17. In the first study, there was a statistically significant



increase in cancer; in the second, a small but significant increase in adult leukemia.

i. Hocking B, Gordon IR, Grain HL, Harfield GE. Cancer incidence and mortality and proximity to TV towers. *Medical J of Australia*. 1995;165:601-605. At extremely low exposure levels, there was an association between increased childhood leukemia incidence and mortality and proximity to TV towers. TV radiation, in the VHF and UHF bands, is similar to but not as harmful as WI-FI radiation at 2.45 GHz.

j. Grayson JK. Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: A nested case-control study. *Am J Epidemiol* 1996; 143:480-6. This study found an association between exposure to ELF and RF/MW radiation and brain tumors.

k. Szmigielski S. Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation. *Sci Total Environ* 1996;180:9-17. This study showed huge increases in leukemia and Non-Hodgkin's lymphomas. Though exposure levels are higher in this study than they would be with school WI-FI, it is possible that certain students or teachers stationed immediately next to the WI-FI infrastructure could receive comparable levels in radiation peaks.

26. Additional studies show neurologic, immune, endocrine, reproductive and cardiac, adverse health effects from low-dose, chronic exposure to RF/MW radiation in humans:

a. Papageorgiou CC, Hountala CD, Maganioti AE, Kyprianou MA, Rabavilas AD, Papadimitriou GN, Capsalis CN. Effects of WI-FI signals on the p300 component of event-related potentials during an auditory hayling task. *J Integr Neurosci* 2011 Jun;10(2):189-202. This study concludes that WI-FI exposure may exert gender-related alterations on neural activity.

- b. Altpeter ES, Roosli M et al. Effect of Short-wave magnetic fields on sleep quality and melatonin cycle in humans: The Schwarzenburg shut-down study. *Bioelectromagnetics* 27:142-150, 2006. Sleep quality improved and melatonin excretion increased when the transmitter was shut down.
- c. Abelin T et al. Sleep disturbances in the vicinity of the short-wave braodcast transmitter Schwarzenburg. *Somnologie* 9:203-209, 2005. There is strong evidence of a causal relationship between operation of a short-wave radio transmitter and sleep disturbances in the surrounding population.
- d. Hutter HP et al. Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. *Occup Environ Med* 2006;63:307-313, 2006. There was a significant relation of some symptoms, especially headaches, to measured power density, as well as effects on wellbeing and performance.
- e. Preece AW, Georgious AG, Duunn EJ, Farrow SC. *Occup Environ Med* 2007 Jun;64(6):402-8. Compared to control village, there were highly significant differences in the reporting of migraine, headache and dizziness military and cell phone antenna systems.
- f. Buchner K, Eger, H. Changes of clinically important neurotransmitters under the influence of modulated RF fields – a long-term study under real-life conditions. *Umwelt-Medizin-Gesellschaft* 24(1):44-57, 2011. There is clear evidence of health-relevant effects, including increase in adrenaline/noradrenaline, subsequent decrease in dopamine from a new MW-emitting base station. During counterregulation, trace amine PEA decreased and remained decreased. Clinically documented increases in sleep problems, cephalgia, vertigo, concentration problems and allergies followed the onset of new microwave transmissions.

- g. Eliyahu I, Luria R, Hareuveny R, Margaliot M, Neiran N and Shani G . Effects of radiofrequency radiation emitted by cellular telephones on the cognitive functions of humans. *Bioelectromagnetics* 27: 119-126: 2006. A total of 36 human subjects were exposed to PM MW and were tested on four distinct cognitive tasks. Exposure to the left side of the brain slows left-hand response time in three of the four tasks.
- h. Barth A, Winker R, Ponocny-Seliger E, Mayrhofer W, Ponocny I, Sauter C and Vana N. *Occup Environ Med* 65: 342-345: 2008. A meta-analysis for neurobehavioural effects due to electromagnetic field exposure emitted by GSM mobile phones. The authors looked at 19 studies of cognitive function in cell phone users, and found in the meta-analysis that there is evidence for a decreased reaction time, altered working memory and increased number of errors in exposed persons.
- i. Augner C, Hacker GW, Oberfeld G, Florian M, Hitzl W, Hutter J and Pauser G. Effects of exposure to base station signals on salivary cortisol, alpha-amylase and immunoglobulin A. *Biomed Environ Sci* 23: 199-207: 2010. This was a human experimental study with exposure to PM MW radiation wherein immune indicators were monitored after five 50-minute sessions. The researchers found dose-dependent changes in cortisol and alpha-amylase.
- j. Avendano C, Mata A, Sanchez Sarimiento CA and Doncel GF. Use of laptop computers connected to internet through WI-FI decreases human sperm motility and increases sperm DNA fragmentation. *Fert Steril*, 2012, In press. In this study human sperm were exposed to WI-FI from a laptop, and were found to show reduced motility after a 4-hour exposure. The results are consistent with other publications (see Agarwal et al., *Fert Steril* 89: 124-128: 2008) that reported that those who use cell phone regularly have reduced sperm count.

k. Baste V, Riise T and Moen BE (2008) *Int J Epidemiol* 37: 369-377; 2008. Radiofrequency electromagnetic fields: male infertility and sex ratio of offspring. This is a study of Norwegian Navy personnel chronically exposed to RF fields on the job. The rates of infertility were related to level of exposure in a dose-dependent fashion.

27. Many toxicologic and other animal studies, of which the following are but a few, support conclusions of cancer, genotoxicity, neurotoxicity and other health outcomes from RF/MW radiation.

a. Sinha R. Chronic non-thermal exposure of modulated 2450 MHz microwave radiation alters thyroid hormones and behavior of male rats. *Int. J. Radiation Biol.* 84:6:505-513, 2008. This study of 2.45 GHz at levels and durations comparable to and less than those of school WI-FI concluded that the radiation was sufficient to alter the levels of thyroid hormone as well as emotional reactivity compared to controls.

b. Nitthy H, Grafstrom G, Tian DP, Malmgren L, Brun A, Persson BRR, Salfors LG and Eberhardt J. *Bioelectromagnetics* 29: 219-232; 2008. This study showed cognitive impairment in rats after long-term exposure to PM MW radiation. This study of rats shows that after 2 hours per week for 55 weeks there was impaired memory for objects in exposed as compared to sham animals.

c. Kimmel S et al. Electromagnetic radiation: Influences on honeybees (*Apis mellifera*). A significant difference between non-exposed and fully irradiated bees was the result of the influence of high-frequency PM RF/MW radiation.

d. Panagopoulos DJ et al. Bioeffects of mobile telephony radiation in relation to its intensity or distance from the antenna. *Int. J Radiat Biol*, 86;(5):345-357, 2010. The PM MW radiations at 900 and 1800 MHz decreased the reproductive capacity by cell death induction, with an increased bioactivity "window" at 10

uW/cm<sup>2</sup>, and still evident down to 1 uW/cm<sup>2</sup>.

e. Everaert J, Bauwens D. A possible effect of electromagnetic radiation from mobile phone base stations on the number of breeding house sparrow (*passer domesticus*). *Electromagnetic Biology and Medicine*, 26:63-72, 2007.

Long-term exposure to higher-level low-intensity PM MW radiation negatively affects the abundance or behavior of House Sparrows in the wild.

f. Magras I, Xenos T. RF Radiation-Induced Changes in the Prenatal Development of Mice. *Bioelectromagnetics* 18:455-461, 1997. Near almost 100 TV and FM broadcast transmitters, with exposure levels between 0.168 uW/cm<sup>2</sup> and 1.053 uW/cm<sup>2</sup>, found in the more exposed groups testicular damage and decreasing size of litters to irreversible infertility.

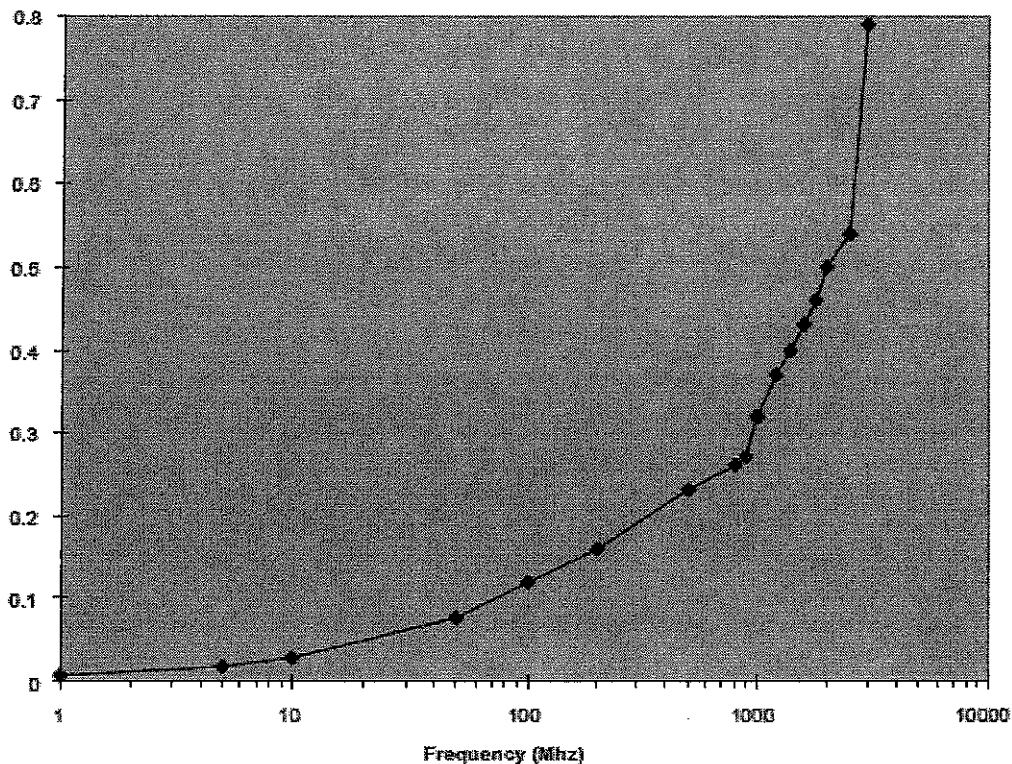
g. Balmori A. Electromagnetic pollution from phone masts. Effects on wildlife, *Pathophysiology* 2009. This large review of wildlife effects concludes, "pulsed telephony microwave radiation can produce effects on nervous, cardiovascular, immune and reproductive systems," including damage to the nervous system by altering EEG and changes to the blood-brain barrier, disruption of the circadian rhythms (sleep-wake) by interfering with the pineal gland and hormonal imbalances, changes in heart rate and blood pressure, impairment of health and immunity towards pathogens, weakness, exhaustion, growth problems, problems in building the nest or impaired fertility, embryonic development, hatching percentage, genetic and developmental problems, problems of locomotion, promotion of tumors and more.

28. Exposure thresholds for harmful effects are lowered in human populations and individuals when duration is increased. Due to the variability of thresholds for harmful effects both in the population and within the individual, there is no exposure power density that is safe. The School's WI-FI deploys arguably the worst possible frequency of 2.45 GHz, that of the

microwave oven, worst because it is most absorbable by the brain and most resonant with the water molecule, such that:

- a. absorption-per-exposure is maximized, dramatically lowering effects thresholds for population and individual effects; and
- b. water molecules in tissues and cells are highly agitated.

**Microwave Absorption in Brain Tissue (Grey Matter)**



Curry, Ph.D., *Wireless LANs in the schoolroom*

29. This above graph, from physicist William Curry PhD's presentation *Wireless LANs in the Schoolroom*, shows how absorption in brain tissue (grey matter) increases exponentially toward the ultra-high frequency (UHF) area of the microwave oven and WI-FI.

30. In the case of the Portland Schools, the additional, unused but still deployed carrier frequency of 5 GHz would likely increase absorption in other, smaller organs, such as the thyroid.

31. The graph also illustrates the problem with the drive of the wireless industry toward ever higher frequencies within the cm microwave band. While nearly all the lower frequency bands have already been allocated by the FCC for specific types of radio transmissions, and transmission of ever more information content on any given channel requires greater bandwidth, each new deployment undermines further the integrity of the population's health. Engineers who design these systems have no training that would qualify them to consider the effects on biologic systems, which is why public health scientists need to be called in to policymaking *prior to* contracting and deployment, not after the fact.

32. The following studies explain the mechanisms of interaction between RF/MW radiation and biologic systems at the cellular level.

- a. The cell membrane recognition process -- which includes signal transduction and 'heat-shock protein' release -- was first discerned by Litovitz and his co-workers at Catholic University of America in the mid-1990s.

Below are a few citations that make the point.

- i. Litovitz, T., C. Montrose, et al. (1994). "Superimposing spatially coherent electromagnetic noise inhibits field induced abnormalities in developing chick embryos." *Bioelectromagnetics* 15(2): 105-113.
- ii. DiCarlo, A., J. Farrell, et al. (1998). "A simple experiment to study electromagnetic field effects: Protection induced by short term exposures to 60 Hz magnetic fields." *Bioelectromagnetics* 19(8): 498-500.
- iii. Penafiel, L., T. Litovitz, et al. (1997). "Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929

- cells." *Bioelectromagnetics* **18**(2): 132-141.
- iv. Dicarlo, A. L., Michael T. Hargis, L. Miguel Penafiel, Theodore A. Litovitz, A. (1999). "Short-term magnetic field exposures (60Hz) induce protection against ultraviolet radiation damage." *International journal of radiation biology* **75**(12): 1541-1549.
  - v. Litovitz, T., C. Montrose, et al. (1990). "Amplitude windows and transiently augmented transcription from exposure to electromagnetic fields." *Bioelectromagnetics* **11**(4): 297-312.
  - vi. Litovitz, T., M. Penafiel, et al. (1997). "The role of temporal sensing in bioelectromagnetic effects." *Bioelectromagnetics* **18**(5): 388-395.
  - vii. Litovitz, T., L. Penafiel, et al. (1997). "Role of modulation in the effect of microwaves on ornithine decarboxylase activity in L929 cells." *Bioelectromagnetics* **18**: 132-141.]
  - viii. Litovitz, T., D. Krause, et al. (1993). "The role of coherence time in the effect of microwaves on ornithine decarboxylase activity." *Bioelectromagnetics* **14**(5): 395-403.
- b. Cell membrane reaction is lipid peroxidation.
    - i. Serban, M. and V. Ni (1994). "Lipid peroxidation and change of plasma lipids in acute ischemic stroke." *Romanian journal of internal medicine= Revue roumaine de médecine interne* **32**(1): 51.



- ii. Vilenko, B., S. Jeney, et al. (2010). "Evidence of lipid peroxidation and protein phosphorylation in cells upon oxidative stress photo-generated by fullerenes." *Biophysical chemistry*.
- iii. Maaroufi, K., E. Save, et al. (2011). "Oxidative stress and prevention of the adaptive response to chronic iron overload in the brain of young adult rats exposed to a 150 kilohertz electromagnetic field." *Neuroscience*.
- iv. Nelson, S. K., S. K. Bose, et al. (1994). "The toxicity of high-dose superoxide dismutase suggests that superoxide can both initiate and terminate lipid peroxidation in the reperfused heart." *Free Radical Biology and Medicine* **16**(2): 195-200.
- v. Alvarez, J. G. and B. T. Storey (1989). "Role of glutathione peroxidase in protecting mammalian spermatozoa from loss of motility caused by spontaneous lipid peroxidation." *Gamete research* **23**(1): 77-90.
- vi. Devasagayam, T., K. Boloor, et al. (2003). "Methods for estimating lipid peroxidation: An analysis of merits and demerits." *Indian journal of biochemistry & biophysics* **40**(5): 300-308.
- c. Free-Radical Damage:
  - i. Ozgur, E., G. Güler, et al. (2010). "Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants n-acetyl cysteine and epigallocatechin-gallate." *International journal of radiation biology*(00): 1-11.

- ii. Gutteridge, J. and X. C. Fu (1981). "Enhancement of bleomycin-iron free radical damage to DNA by antioxidants and their inhibition of lipid peroxidation." *FEBS letters* **123**(1): 71.
- d. mRNA:
  - i. Yan, J. G., M. Agresti, et al. (2009). "Qualitative Effect on mRNAs of Injury-Associated Proteins by Cell Phone Like Radiation in Rat Facial Nerves. *Electromagnetic Biology and Medicine* **28**(4): 383-390.
  - ii. Yan, J. G., M. Agresti, et al. (2008). "Upregulation of specific mRNA levels in rat brain after cell phone exposure." *Electromagnetic Biology and Medicine* **27**(2): 147-154.
  - iii. Simbürger, E., A. Stang, et al. (1997). "Expression of connexin43 mRNA in adult rodent brain." *Histochemistry and cell biology* **107**(2): 127-137.
  - iv. Chen, J., H. C. He, et al. (2010). "Effects of Pulsed Electromagnetic Fields on the mRNA Expression of RANK and CAII in Ovariectomized Rat Osteoclast-Like Cell." *Connective Tissue Research* **51**(1): 1-7.
- e. Epigenetic changes.... environmentally induced genetic change:
  - i. Migliore, L. and F. Copped (2009). "Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases." *Mutation Research/Fundamental and Molecular*

*Mechanisms of Mutagenesis* **667**(1-2): 82-97.

- ii. Currenti, S. (2009). "Understanding and Determining the Etiology of Autism." *Cellular and Molecular Neurobiology* **30**(2): 161-171.
- f. Micronuclei formation:
  - i. Tice, R. R., G. G. Hook, et al. (2002). "Genotoxicity of radiofrequency signals. I. Investigation of DNA damage and micronuclei induction in cultured human blood cells." *Bioelectromagnetics*, **23**(2): 113-126.
  - ii. Lerchl, A. (2009). "Comments on "Radiofrequency electromagnetic fields (UMTS, 1,950 MHz) induce genotoxic effects in vitro in human fibroblasts but not in lymphocytes" by Schwarz et al. (Int Arch Occup Environ Health 2008: doi: 10.1007/s00420-008-0305-5)." *Int Arch Occup Environ Health* **82**(2): 275-278.
  - iii. Vijayalaxmi and T. J. Prihoda (2009). "Genetic damage in mammalian somatic cells exposed to extremely low frequency electro-magnetic fields: a meta-analysis of data from 87 publications (1990-2007)." *Int J Radiat Biol* **85**(3): 196-213.
  - iv. Sannino, A., M. Sarti, et al. (2009). "Induction of adaptive response in human blood lymphocytes exposed to radiofrequency radiation." *Radiat Res* **171**(6): 735-742.
- g. DNA repair disruption:
  - i. Brusick, D., R. Albertini, et al. (1998). "Genotoxicity of radiofrequency radiation. DNA/Genetox Expert Panel." *Environ*

*Mol Mutagen* 32(1): 1-16.

- ii. Belyaev, I. Y., E. Markova, et al. (2009). "Microwaves from UMTS/GSM mobile phones induce long-lasting inhibition of 53BP1/gamma-H2AX DNA repair foci in human lymphocytes." *Bioelectromagnetics* 30(2): 129-141.
- iii. Sun, L. X., K. Yao, et al. (2006). "[Effect of acute exposure to microwave from mobile phone on DNA damage and repair of cultured human lens epithelial cells in vitro]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 24(8): 465-467.
- h. Immune response suppression:
  - i. Lyle, D. B., P. Schechter, et al. (1983). "Suppression of T-lymphocyte cytotoxicity following exposure to sinusoidally amplitude-modulated fields." *Bioelectromagnetics* 4(3): 281-292.
  - ii. Elekes, E., G. Thuroczy, et al. (1996). "Effect on the immune system of mice exposed chronically to 50 Hz amplitude-modulated 2.45 GHz microwaves." *Bioelectromagnetics* 17(3): 246-248.
  - iii. DABALA, D., D. SURCEL, et al. (2008). "Oxidative and Immune Response in Experimental Exposure to Electromagnetic Fields." *Electromagnetic field, health and environment: proceedings of EHE'07*: 105.
  - iv. Surcel, D., D. Dabala, et al. (2009). "Free Radicals, Lipid Peroxidation and Immune Response in Experimental Exposure to Electromagnetic Fields." *Epidemiology* 20(6): S118.

## **Conclusions**

33. To understand the seriousness of this Agent of PM RF/MW radiation in interaction with populations and individuals, we need to consider some basic facts in addition to the many relevant and reliable studies above. For example, where shortwave, AM, FM, TV and cell phone infrastructure frequencies are demonstrated to be harmful, as they consistently are shown to be at low intensities with long duration, then, all other factors being equal, MW radiation at 2.45 GHz will likely be more harmful yet, due to its higher absorption-per-exposure and water molecule resonance. Increasing the constancy and length of exposure toward the maximum of occupational and 24-7 durations will lower the threshold for effects in populations and individuals. Complex radiation microenvironments with pulse-modulated wave and multiple sources, such as are deployed in WI-FI-equipped schools, are more harmful than a single, isolated MW radiation exposure at the same power density and duration. There are only a few of the many studies of RF/MW radiation infrastructure such as base stations that fail to show their studied effect. However, even were the reverse true, i.e., if there existed greater number than those that do show adverse effects, it is the case that positive studies (those that show adverse effects) hold more weight than negative studies (those that show no effect).

34. The FCC-appointed guideline-setting Commission, ASTM-IEEE, in 1991 referred in its conclusions to RF/MW radiation, the Agent, as a 'Hazard,' specifically setting a 'Hazard Threshold.' It has been discovered that, even amongst the 120 studies chosen by the Committee to prove the validity of its Hazard Threshold, there were 15 studies that concluded adverse effects at levels *lower* than the Hazard Threshold, thus disproving its validity. Three of these studies actually showed adverse effects at less than 10 percent of the Hazard Threshold. Thus the guidelines have no credibility.

35. The large body of scientific literature moreover redundantly proves this Agent to be a hazard. The media-promulgated notion that the relevant scientific studies are inconsistent and inconclusive is false and misleading. Chronic exposure to PM MW radiation harms every individual in a population in some ways, even if these are not always detectable by the individual or consciously attributed to the responsible RF/MW radiation sources. This Agent injures some individuals into a condition in which symptoms will be more easily retriggered with subsequent exposure. And for *a priori* susceptible individuals and those using electronic medical devices, it can respectively exacerbate the extant medical conditions and disrupt medical device operation, even to the point of death. Bassen 1997 discusses the hundreds of excess deaths, even at that time, from wireless communications radiation. See also *Radiofrequency Interference with Medical Devices*, IEEE Engineering in Medicine and Biology Magazine 17(3):111-114(1998), <http://ewh.ieee.org/soc/embs/comar/interfer.htm>.

36. For these reasons, WI-FI must be banned from school deployment.

37. I will receive no compensation for my testimony beyond out-of-pocket expenses.

Dated this 20<sup>th</sup> day of December, 2011.



---

DR. DAVID O. CARPENTER, M.D.  
Director, Institute for Health and the Environment  
University at Albany

## ***CURRICULUM VITAE***

Name: David O. Carpenter

Home Address: 2749 Old State Road  
Schenectady, New York 12303

**Positions Held:**

Director, Institute for Health and the Environment  
University at Albany  
Professor, Environmental Health Sciences  
School of Public Health, University at Albany  
5 University Place, A217, Rensselaer, NY 12144

Education: 1959 B.A., Harvard College, Cambridge, MA  
1964 M.D., Harvard Medical School, Boston, MA

**Positions Held:**

9/61-6/62 Research Fellow, Department of Physiology, University of Göteborg, Sweden with Professor Anders Lundberg  
7/64-6/65 Research Associate, Department of Physiology, Harvard Medical School, Boston, MA under the direction of Dr. Elwood Henneman  
7/65-2/73 Neurophysiologist, Laboratory of Neurophysiology, National Institutes of Mental Health, Dr. Edward V. Evarts, Chief, Assistant Surgeon, USPHS, currently a Reserve Officer in the USPHS.  
2/73-3/80 Chairman, Neurobiology Department Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, Bethesda, MD  
3/80-9/85 Director, Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, NY  
9/85-1/98 Dean, School of Public Health, University at Albany  
9/85-Pres. Professor, Departments of Environmental Health Sciences and Biomedical Sciences, School of Public Health, University at Albany.  
9/85-7/98 Research Physician, Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, NY  
1/98-1/05 Adjunct Professor in the Center for Neuropharmacology & Neuroscience, Albany Medical College, Albany, NY  
2001-Pres. Director, Institute for Health and the Environment, University at Albany, SUNY, Rensselaer, NY. The Institute was named a Collaborating Center of the World Health Organization in 2011.  
2005-Pres. Senior Fellow, Alden March Bioethics Institute, Albany Medical College/Center, Albany, New York  
**Editor-in-Chief:** Cellular and Molecular Neurobiology, 1981 - 1987  
**Editorial Advisor:** Cellular and Molecular Neurobiology, 1987 - Present  
**Editorial Boards:** Journal of Public Health Management and Practice, 1995 - 2002  
International Journal of Occupational Medicine & Environmental Health  
1996 - Present

Journal of Alzheimer's Disease – Associate Editor, 2007-2009  
Reviews in Environmental Health; 2008-present  
International Archives of Occupational and Environmental Health; 2009-present.  
Journal of Environmental and Public Health, 2009-present.  
Environmental Health Perspectives, 2010-present

**National and International Committees:**

- 1978, 1981 Physiology Study Section (Ad hoc member)
- 1979-1985 NIH International Fellowship Study Section
- 1974-1981 Member, Steering Committee of the Section on the Nervous System, American Physiological Society (Chairman of the Committee, 9/76-4/80)
- 1981-1989 Member, USA National Committee for the International Brain Research Organization
- 1985-1986 Committee on Electric Energy Systems of the Energy Engineering Board, National Research Council
- 1986-1987 Member, Neurophysiology Peer Panel for the National Aeronautics and Space Administration
- 1987-1989 Member, Science Advisory Council of the American Paralysis Association
- 1987-1990 Advisory Panel for the Electric Energy System Division, U.S. Department of Energy
- 1985-1993 Committee #79, National Council on Radiation Protection and Measurements
- 1986-1997 Member, Legislative and Education Committees, Association of Schools of Public Health
- 1989-1994 Member, Neuroscience Discipline Working Group, Life Sciences Division of the NASA
- 1994, 1995 Federation of American Societies for Experimental Biology Consensus Conference on FY 1995 Federal Research Funding
- 1994-1997 Member, Legislative Committee of the Association of Schools of Public Health
- 1997 Member, Executive Committee of the Association of Schools of Public Health
- 1997-2000 National Advisory Environmental Health Sciences Council of the National Institutes of Health
- 1998-Pres. Member, U.S. Section of the Great Lakes Science Advisory Board of the International Joint Commission
- 2000-Pres. Member, Board of Directors, Pacific Basin Consortium for Hazardous Waste Health and Environment; Treasurer, 2001-2004, 2008-pres; Chair, 2004-2008
- 2001-2008 United States Co-Chair, Workgroup on Ecosystem Health of the Science Advisory Board of the International Joint Commission
- 2002-2003 Member, Committee on the Implications of Dioxin in the Food Supply, The National Academies, Institute of Medicine
- 2003-2008 Member, United States Environmental Protection Agency, Children's Health Protection Advisory Committee
- 2003-Pres. Chair, Advisory Committee to the World Health Organization and National Institute of Environmental Health Sciences on collaborative activities.
- 2007-2011 Chair, Workgroup on Risks vs. Benefits of Fish Consumption, Science Advisory Board, International Joint Commission.



### State and Local Committees:

- 1980-1987 Executive Secretary, New York State Power Lines Project  
1985-1989 Board of Scientific Advisors, Institute of Basic Research, OMRDD, N.Y.  
1986-1989 Member, Steering Committee, Health Policy and Administrative Consortium of the Capital District  
1991-1992 Member, Connecticut Academy of Sciences and Engineering Committee on Electromagnetic Field Health Effects  
1991-1992 Member, Board of Directors of the Capital District Chapter of the Alzheimer's Disease and Related Disorders Association, Inc.  
1991-1992 Member, State Task Force for the Reform of Middle Level Education in NY State  
1992-1993 Member, State Needs Task Force on Health Care and Education  
1987-1998 Delegate-at-Large, New York State Public Health Association  
1991-1995 Member, Board of Directors of the Capital District Amyotrophic Lateral Sclerosis Association  
1994 Chair, Council of Deans, University at Albany, SUNY  
1997-2008. Member, Board of Directors, (Chair 1998-2004) Albany-Tula Inc.: A Capital Region Alliance  
2000-Pres. Member, Board of Directors, Healthy Schools Network, Inc.  
2000-2003 Member, Medical Advisory Board, Hepatitis C Coalition, New York  
2000-2004 Member, Environmental Protection Agency /National Association of State Universities and Land Grant Colleges Task Force  
2001-2008 Member, Board of Directors, Environmental Advocates of New York  
2004-2007 Member, Ad Hoc Advisory Group on Brownfield Cleanup Standards  
2005-Pres. Member, Schooling Chefs Curriculum Advisory Board  
2005-2008 Member, Board of Directors, Citizens Environmental Coalition  
2006-2009 Member, Board of Directors, Marine Environmental Research Institute  
2007-2009 Member, New York State Renewable Energy Task Force

### Honors, Awards and Fellowships:

- 1959 B.A. awarded magna cum laude. Thesis entitled "Metamorphosis of visual pigments: A study of visual system of the salamander, *Ambystoma tigrinum*" (Thesis advisor, Professor George Wald)  
Elected to Phi Beta Kappa and to Sigma Xi  
1964 M.D. awarded cum laude for a thesis in a special field. Thesis entitled "Electrophysiological observations on the importance on neuron size in determining responses to excitation and inhibition in motor and sensory systems" (Thesis advisor, Dr. Elwood Henneman)  
1964 Awarded the Leon Resnick Prize given to a Harvard Medical School graduate showing promise in research  
1970 Awarded the Moseley Traveling Fellowship for study in England (Fellowship declined)  
1971 Invited as Visiting Professor of Physiology, Centro de Investigacion y de Estudios Avanzados, del Institute Politecnico Nacional, Mexico 14, D.F., Mexico, for 3 months

- 1982, 1986 Visiting Professor of Physiology, Department of Physiology, Kyushu
- 1987 University, Fukuoka, Japan, for a period of three months each
- 1989 Awarded Jacob Javits Neuroscience Investigator Award from the National  
Institute of Neurological and Communicative Diseases and Stroke
- 1999 Awarded Homer N. Calver Award from the American Public Health  
Association for studies in environmental health.
- 2001 Awarded 2001 Academic Laureate from the University at Albany  
Foundation.
- 2010 Awarded the Albion O. Bernstein, M.D. Award in recognition of an  
outstanding contribution to public health and the prevention of disease through  
lifelong research of environmental health hazards and for limitless devotion to  
medical education by the Medical Society of the State of New York.

**Federal Grants Held: (Principal Investigator Only)**

- 1980-1983 United States Air Force, "Mechanisms of Radiation-Induced Emesis in Dogs",  
\$76,847 total direct costs.
- 1982-1988 National Institute of Health, "Mechanisms of Desensitization at Central Synapses",  
\$464,786 total direct costs.
- 1984-1986 Defense Nuclear Agency, "Mechanisms of Radiation-Induced Emesis in Dogs",  
\$330,504 total direct costs.
- 1986-1996 National Institute of Health, "Mechanisms of Excitatory Amino Acids Actions and  
Toxicity", 1986-1989 \$231,848 total direct costs; 1990-1996 \$562,926 total direct  
costs.
- 1989-1993 National Institute of Health, "Mechanisms of Lead Neurotoxicity" \$373,576 total  
direct costs
- 1990-1995 National Institute of Environmental Health Sciences, Superfund Basic Research  
Program, "Multidisciplinary Study of PCBs and PCDFs at a Waste Site", D.O.  
Carpenter, P.I. \$5,783,419 total direct costs.
- 1995-2001 Fogarty International Center, National Institutes of Health, International Training  
Program in Environmental and Occupational Health. A Central/Eastern European  
Environ/Occup Training Program, D.O. Carpenter, P.I. \$657,520 total costs.
- 1995-2001 National Institute of Environmental Health Sciences, Superfund Basic Research  
Program, "Multidisciplinary Study of PCBs," D.O. Carpenter, P.I. \$12,653,709 total  
direct costs.
- 1998-1999 Environmental Protection Agency, A Indoor Air Risk at Akwesasne - Pilot Project, D.O.  
Carpenter, P.I. \$9,996 total costs.
- 2000-2002 Association Liaison Office for University Cooperation in Development,  
A Cooperative Program in Environmental Health between the Institute of Public  
Health at Makerere University, Kampala, Uganda and the School of Public Health,  
University at Albany, USA, D.O. Carpenter, P.I. \$96,432 total costs.
- 2001-2007 Fogarty International Center, National Institutes of Health, International Training  
Program in Environmental and Occupational Health. A Multidisciplinary  
Environmental Health Training, D.O. Carpenter, P.I. \$850,000 total costs.
- 2006-2011 Pakistan-US Science and Technology Cooperative Program (US National  
Academy of Sciences). "Association of particulate matter with daily morbidity in

- an urban population,” D.O. Carpenter, P.I., \$391,104 total costs.
- 2009-2013 Exploratory Center on Minority Health and Health Disparities in Smaller Cities. Project 2: Environmental contaminants and reproductive health of Akwesasne Mohawk women. \$387,825 for year 1. D.O. Carpenter, Co-PI.
- 2010-2013 Department of the Army, “Gulf War Illness: Evaluation of an Innovative Detoxification Program: D.O. Carpenter, P.I., \$636,958 total costs.
- 2010-2013 Higher Education for Development of the United States Agency for International Development, “Drinking Water Supply, Sanitation, and Hygiene Promotion : Health Interventions in Two Urban Communities of Kampala City and Mukono Municipality, Uganda”. D. O. Carpenter, P.I., \$299,736 total costs.
- 2011-2016 National Institute of Environmental Health Sciences (1R01ES019620), “Protecting the health of future generations: Assessing and preventing exposures.” PK Miller, FA von Hippel, CL Buck and DO Carpenter, Co-P.I.s, \$471,521 for the period 8/08/11-4/30/12, \$2,354,871 for the period 2011-2016.

#### **Research Interests:**

- Exposure to persistent organic pollutants and risk of diabetes, cardiovascular disease, and hypertension.
- Cognitive and behavioral effects of environmental contaminants on children (IQ, ADHD) and older adults (dementias, Parkinson’s Disease and ALS).
- Ionizing and non-ionizing radiation biology.
- Effects of air pollution on respiratory and cardiovascular function.

#### **Other Professional Activities:**

Host, The Public Radio Health Show (a 30 min public health information show carried on 170+ stations nationwide), plus the Armed Forces Radio Network and Voice of America, 1985-2001. Authored a biweekly health column in The Troy Record, a local newspaper, 1997-1999.

#### **Major Peer-Reviewed Publications:**

1. Carpenter, D.O., Lundberg, A. and Norrsell, U. Effects from the pyramidal tract on primary afferents and on spinal reflex actions to primary afferents. *Experientia*, 18:337, 1962.
2. Carpenter, D.O., Engberg, I. and Lundberg, A. Presynaptic inhibition in the lumbar cord evoked from the brain stem. *Experientia*, 18:450, 1962.
3. Carpenter, D.O., Lundberg, A. and Norrsell, U. Primary afferent depolarization evoked from the sensorimotor cortex. *Acta Physiol. Scand.*, 59:126-142.
4. Carpenter, D.O., Engberg, I., Funkenstein, H. and Lundberg, A. Decerebrate control of reflexes to primary afferents. *Acta Physiol. Scand.*, 59:424-437, 1963.
5. Carpenter, D.O., Engberg, I. and Lundberg, A. Differential supraspinal control of inhibitory and excitatory actions from the FRA to ascending spinal pathways. *Acta Physiol. Scand.*, 63:103-110, 1965.

6. Henneman, E., Somjen, G.G. and Carpenter, D.O. Excitability and inhibibility of motoneurons of different sizes. *J. Neurophysiol.*, 28:599-620, 1965.
7. Henneman, E., Somjen, G.G. and Carpenter, D.O. Functional significance of cell size in spinal motoneurons. *J. Neurophysiol.*, 28:560-580, 1965.
8. Somjen, G.G., Carpenter, D.O. and Henneman, E. Selective depression of alpha motoneurons of small size by ether. *J. Pharmacol.*, 148:380-385, 1965.
9. Somjen, G., Carpenter, D.O. and Henneman, E. Response of motoneurons of different sizes to graded stimulation of supraspinal centers of the brain. *J. Neurophysiol.*, 28:958-965, 1965.
10. Carpenter, D.O., Engberg, I. and Lundberg, A. Primary afferent depolarization evoked from the brain stem and the cerebellum. *Arch. Ital. Biol.*, 104:73-85, 1966.
11. Carpenter, D.O. and Henneman, E. A relation between the threshold of stretch receptors in skeletal muscle and the diameter of axons. *J. Neurophysiol.*, 29:353-368, 1966.
12. Carpenter, D.O. Temperature effects on pacemaker generation, membrane potential, and critical firing threshold in *Aplysia* neurons. *J. Gen. Physiol.*, 50:1469-1484, 1967.
13. Chase, T.N., Breese, G., Carpenter, D., Schanberg, S. and Kopin, I. Stimulation-induced release of serotonin from nerve tissue. *Adv. Pharmacol.*, 6A:351-364, 1968.
14. Carpenter, D.O. and Alving, B.O. A contribution of an electrogenic  $\text{Na}^+$  pump to membrane potential in *Aplysia* neurons. *J. Gen. Physiol.*, 52:1-21, 1968.
15. Olson, C.B., Carpenter, D.O. and Henneman, E. Orderly recruitment of muscle action potentials. *Arch. Neurol.*, 19:591-597, 1968.
16. Carpenter, D.O. Membrane potential produced directly by the  $\text{Na}^+$  pump in *Aplysia* neurons. *Comp. Biochem. Physiol.*, 35:371-385, 1970.
17. Carpenter, D.O. and Gunn, R. The dependence of pacemaker discharge of *Aplysia* neurons upon  $\text{Na}^+$  and  $\text{Ca}^{++}$ . *J. Cell. Physiol.*, 75:121-127, 1970.
18. Kraus, K.R., Carpenter, D.O. and Kopin, I. R. Acetylcholine-induced release of norepinephrine in the presence of tetrodotoxin. *J. Pharmacol. Exp. Therap.*, 73:416-421, 1970.
19. Barker, J.L. and Carpenter, D.O. Thermosensitivity of neurons in the sensorimotor cortex of the cat. *Science*, 169:597-598, 1970.
20. Carpenter, D.O., Hovey, M.M. and Bak, A. Intracellular conductance of *Aplysia* neurons and squid axon as determined by a new technique. *Intl. J. Neurosci.*, 2:35-48, 1971.
21. Carpenter, D.O., Breese, G., Schanberg, S. and Kopin, I. Serotonin and dopamine: Distribution and accumulation in *Aplysia* nervous and non-nervous tissues. *Int. J. Neurosci.*, 2:49-56, 1971.
22. Hovey, M.M., Bak, A.F. and Carpenter, D.O. Low internal conductivity of *Aplysia* neuron somata. *Science*, 176:1329-1331, 1972.
23. Carpenter, D.O. Electrogenic sodium pump and high specific resistance in nerve cell bodies of the squid. *Science*, 179:1336-1338, 1973.
24. Carpenter, D.O. and Rudomin, P. The organization of primary afferent depolarization in the isolated spinal cord of the frog. *J. Physiol. (Lond.)*, 229:471-493, 1973.
25. Shain, W., Green, L.A., Carpenter, D.O., Sytkowski, A.J. and Vogel, Z. *Aplysia* acetylcholine receptors: Blockage by and binding of  $\alpha$ -bungarotoxin. *Brain Res.*, 72:225-240, 1974.
26. Pierau, Fr.-K., Torrey, P. and Carpenter, D.O. Mammalian cold receptor afferents: Role of an electrogenic sodium pump in sensory transduction. *Brain Res.*, 73:156-160, 1974.

27. Saavedra, J.M., Brownstein, M.J., Carpenter, D.O. and Axelrod, J. Octopamine: Presence in single neurons in *Aplysia* suggests neurotransmitter function. *Science*, 185:364-365, 1974.
28. Willis, J.A., Gaubatz, G.L. and Carpenter, D.O. The role of the electrogenic sodium pump in modulation of pacemaker discharge of *Aplysia* neurons. *J. Cell. Physiol.*, 84:463-472, 1974.
29. Brownstein, M.J., Saavedra, J.M., Axelrod, J., Zeman, G.H. and Carpenter, D.O. Coexistence of several putative neurotransmitters in single identified neurons of *Aplysia*. *Proc. Natl. Acad. Sci. (USA)*, 71:4662-4665, 1975.
30. Carpenter, D.O. and Gaubatz, G.L. Octopamine receptors on *Aplysia* neurons mediate hyperpolarization by increasing membrane conductance. *Nature*, 252:483-485, 1974.
31. Pierau, Fr.-K., Torrey, P. and Carpenter, D.O. Afferent nerve fiber activity responding to temperature changes of the scrotal skin of the rat. *J. Neurobiol.*, 38:601-612, 1975.
32. Carpenter, D.O. and Gaubatz, G.L. H<sub>1</sub> and H<sub>2</sub> histamine receptors on *Aplysia* neurons. *Nature*, 254:343-344, 1975.
33. Carpenter, D.O., Hovey, M.M. and Bak, A.F. Resistivity of axoplasm. II. Internal resistivity of giant axons of squid and *Myxicola*. *J. Gen. Physiol.*, 66:139-148, 1975.
34. Zeman, G.H. and Carpenter, D.O. Asymmetric distribution of aspartate in ganglia and single neurons of *Aplysia*. *Comp. Biochem. Physiol.*, 52C:23-26, 1975.
35. Pierau, Fr.-K., Torrey, P. and Carpenter, D.O. Effect of ouabain and potassium-free solution on mammalian thermosensitive afferents *in vitro*. *Pflugers Arch.*, 359:349-356, 1975.
36. Swann, J.W. and Carpenter, D.O. The organization of receptors for neurotransmitters on *Aplysia* neurons. *Nature*, 258:751-754, 1975.
37. Yarowsky, P.J. and Carpenter, D.O. Aspartate: distinct receptors on *Aplysia* neurons. *Science*, 192:806-809, 1976.
38. Foster, K.R., Bidinger, J.M. and Carpenter, D.O. The electrical resistivity of aqueous cytoplasm. *Biophys. J.*, 16:991-1001, 1976.
39. Carpenter, D.O., Greene, L.A., Shain, W. and Vogel, Z. Effects of eserine and neostigmine on the interaction of  $\alpha$ -bungarotoxin with *Aplysia* acetylcholine receptors. *Mol. Pharmacol.*, 12:999-1006, 1976.
40. Saavedra, J.M., Ribas, J., Swann, J. and Carpenter, D.O. Phenylethanolamine: A new putative neurotransmitter in *Aplysia*. *Science*, 195:1004-1006, 1977.
41. Carpenter, D.O., Swann, J.W. and Yarowsky, P.J. Effect of curare on responses to different putative neurotransmitters in *Aplysia* neurons. *J. Neurobiol.*, 8:119-132, 1977.
42. Yarowsky, P.J. and Carpenter, D.O. GABA mediated excitatory responses on *Aplysia* neurons. *Life Sci.*, 20:1441-1448, 1977.
43. Willis, J.A., Myers, P.R. and Carpenter, D.O. An ionophoretic module which controls electroosmosis. *J. Electrophysiol. Tech.*, 6:34-41, 1977.
44. Yarowsky, P.J. and Carpenter, D.O. Receptors for gamma-aminobutyric acid (GABA) on *Aplysia* neurons. *Brain Res.*, 144:75-94, 1978.
45. Carpenter, D.O., Gaubatz, G., Willis, J.A. and Severance, R. Effects of irradiation of *Aplysia* pacemaker neurons with 20 MeV electrons. *Rad. Res.*, 76:32-47, 1978.
46. Yarowsky, P.J. and Carpenter, D.O. A comparison of similar ionic responses to gamma-aminobutyric acid and acetylcholine. *J. Neurophysiol.*, 41:531-541, 1978.
47. Blum, B., Aufer, C.R. and Carpenter, D.O. A head holder and stereotaxic device for the rattlesnake. *Brain Res. Bull.*, 3:271-274, 1978.

48. Swann, J.W., Sinback, C.N. and Carpenter, D.O. Dopamine-induced muscle contractions and modulation of neuromuscular transmission in *Aplysia*. *Brain Res.*, 157:167-172, 1978.
49. Swann, J.W., Sinback, C.N. and Carpenter, D.O. Evidence for identified dopamine motor neurons to the gill of *Aplysia*. *Neurosci. Lett.*, 10:275-280, 1978.
50. Keibarian, P.R., Keibarian, J.W. and Carpenter, D.O. Regulation of cyclic AMP in heart and gill of *Aplysia* by the putative neurotransmitters, dopamine and serotonin. *Life Sci.*, 24:1757-1764, 1979.
51. Carpenter, D.O. Interchangeable association of neurotransmitter receptors with several ionophores. *Brain Res. Bull.*, 4:149-152, 1979.
52. Pellmar, T.C. and Carpenter, D.O. Voltage-dependent calcium current induced by serotonin. *Nature*, 277:483-484, 1979.
53. Ruben, P.C., Swann, J.W. and Carpenter, D.O. Neurotransmitter receptors on gill muscle fibers and the gill peripheral nerve plexus in *Aplysia*. *Canad. J. Physiol. Pharmacol.*, 57:1088-1097, 1979.
54. Pellmar, T.C. and Carpenter, D.O. Serotonin induces a voltage-sensitive calcium current in neurons of *Aplysia californica*. *J. Neurophysiol.*, 44:423-439, 1980.
55. Parver, L.M., Auker, C. and Carpenter, D.O. Choroidal blood flow as a heat dissipating mechanism in the macula. *Am. J. Ophthalmol.*, 89:641-646, 1980.
56. Mell, L.D., Jr. and Carpenter, D.O. Fluorometric determination of octopamine in tissue homogenates by high-performance liquid chromatography. *Neurochem. Res.*, 5:1089-1096, 1980.
57. Braitman, D.J., Auker, C.R. and Carpenter, D.O. Thyrotropin-releasing hormone has multiple actions in cortex. *Brain Res.*, 194:244-248, 1980.
58. Meszler, R.M., Auker, C.R. and Carpenter, D.O. Fine structure and organization of the infrared receptor relay, the lateral descending nucleus of the trigeminal nerve in pit vipers. *J. Comp. Neurol.*, 196:571-584, 1981.
59. Auker, C.R., Parver, L.M., Doyle, T. and Carpenter, D.O. Choroidal blood flow: I. Ocular tissue temperature as a measure of flow. *Arch. Ophthalmol.*, 100:1323-1326, 1982.
60. Parver, L.M., Auker, C., Carpenter, D.O. and Doyle, T. Choroidal blood flow: II. Reflexive control in the monkey. *Arch. Ophthalmol.*, 100:1327-1330, 1982.
61. Hori, N., Auker, C.R., Braitman, D.J. and Carpenter, D.O. Lateral olfactory tract transmitter: Glutamate, aspartate or neither? *Cell. Mol. Neurobiol.*, 1:115-120, 1981.
62. Scappaticci, K.A., Dretchen, K.L., Carpenter, D.O. and Pellmar, T.C. Effects of furosemide on neural mechanisms in *Aplysia*. *J. Neurobiol.*, 12:329-341, 1981.
63. Pellmar, T.C. and Carpenter, D.O. Cyclic AMP induces a voltage-dependent current in neurons of *Aplysia californica*. *Neurosci. Lett.*, 22:151-157, 1981.
64. Parver, L., Auker, C. and Carpenter, D.O. Stabilization of macular temperature: The stabilizing effect of the choroidal circulation on the temperature environment of the macula. *Retina*, 2:117-120, 1982.
65. Green, R.W. and Carpenter, D.O. Biphasic responses to acetylcholine in mammalian reticulospinal neurons. *Cell. Molec. Neurobiol.*, 1:401-405, 1981.
66. Hori, N., Auker, C.R., Braitman, D.J. and Carpenter, D.O. Pharmacologic sensitivity of amino acid responses and synaptic activation of *in vitro* prepyriform neurons. *J. Neurophysiol.*, 48:1289-1301, 1982.
67. Slater, N.T. and Carpenter, D.O. Blockade of acetylcholine-induced inward currents in *Aplysia* neurons by strychnine and desipramine: effect of membrane potential. *Cell. Molec. Neurobiol.*, 2:53-58, 1982.

68. Swann, J.W., Sinback, C.N., Pierson, M.G. and Carpenter, D.O. Dopamine produces muscle contractions and modulates motoneuron-induced contractions in *Aplysia* gill. Cell. Molec. Neurobiol., 2:291-308, 1982.
69. Swann, J.W., Sinback, C.N., Keabian, P.R. and Carpenter, D.O. Motoneurons which may utilize dopamine as their neurotransmitter. Cell. Molec. Neurobiol., 2:309-324, 1982.
70. Auker, C.R., Meszler, R.M. and Carpenter, D.O. Apparent discrepancy between single unit activity and <sup>14</sup>C-deoxyglucose labelling in the optic tectum of the rattlesnake. J. Neurophysiol., 49:1504-1516, 1983.
71. Slater, N.T., Carpenter, D.O., Freedman, J.E. and Snyder, S.H. Vipoxin both activates and antagonizes three types of acetylcholine response in *Aplysia* neurons. Brain Res., 278:266-270, 1983.
72. ffrench-Mullen, J.M.H., Hori, N., Nakanishi, H., Slater, N.T. and Carpenter, D.O. Assymmetric distribution of acetylcholine receptors and M channels on prepyriform neurons. Cell. Molec. Neurobiol., 3:163-182, 1983.
73. Carpenter, D.O., Briggs, D.B. and Strominger, N. Responses of neurons of canine area postrema to neurotransmitters and peptides. Cell. Molec. Neurobiol., 3:113-126, 1983.
74. Slater, N.T. and Carpenter, D.O. Blocking kinetics at excitatory acetylcholine responses on *Aplysia* neurons. Biophys. J., 45:24-25, 1984.
75. Chesnut, T.J. and Carpenter, D.O. Two-component desensitization of three types of responses to acetylcholine in *Aplysia*. Neurosci. Lett., 39:285-290, 1983.
76. Haas, H.L., Jeffreys, J.G.R., Slater, N.T. and Carpenter, D.O. Modulation of low calcium induced field bursts in the hippocampus by monoamines and cholinomimetics. Pflugers Arch., 400:28-33, 1984.
77. Parvar, L.M., Auker, C.R. and Carpenter, D.O. Choroidal blood flow. III. Reflexive control in human eyes. Arch. Ophthalmol., 101:1604-1606, 1983.
78. Slater, N.T., Haas, H.L. and Carpenter, D.O. Kinetics of acetylcholine-activated cation channel blockade by the calcium antagonist D-600 in *Aplysia* neurons. Cell. Molec. Neurobiol., 3:329-344, 1983.
79. McCreery, M.J. and Carpenter, D.O. Modulation of neuronal responses to L-glutamate in *Aplysia*. Cell. Molec. Neurobiol., 4:91-95, 1984.
80. Carpenter, D.O., Briggs, D.B. and Strominger, N. Peptide-induced emesis in dogs. Behav. Brain Res., 11:277-281, 1984.
81. ffrench-Mullen, J.M.H., Hori, N. and Carpenter, D.O. N-methyl-D-aspartate and L-aspartate activate distinct receptors in prepyriform cortex. Cell. Molec. Neurobiol., 4:185-189, 1984.
82. Slater, N.T. and Carpenter, D.O. A study of the cholinolytic actions of strychnine using the technique of concentration jump relaxation analysis. Cell. Molec. Neurobiol., 4:263-271, 1984.
83. Slater, N.T., Hall, A.F. and Carpenter, D.O. Kinetic properties of cholinergic desensitization in *Aplysia* neurons. Proc. Roy. Soc. Lond. B, 223:63-78, 1984.
84. Akaike, N., Hattori, K., Oomura, Y. and Carpenter, D.O. Bicuculline and picrotoxin block gamma-aminobutyric acid-gated Cl<sup>-</sup> conductance by different mechanisms. Experientia, 41:70-71, 1985.
85. Slater, N.T., Carpenter, D.O., Freedman, J.E. and Snyder, S.H. Dual effects of the snake venom polypeptide vipoxin on receptors for acetylcholine and biogenic amines in *Aplysia* neurons. Neurosci., 14:723-733, 1985.

86. Mizuno, Y., Oomura, Y., Hori, N. and Carpenter, D.O. Action of vasopressin on CA1 pyramidal neurons in rat hippocampal slices. *Brain Res.*, 309:241-246, 1984.
87. Slater, N.T., Hall, A.F. and Carpenter, D.O. Trifluoperazine and calcium antagonists accelerate cholinergic desensitization in *Aplysia* neurons. *Brain Res.*, 329:275-279, 1985.
88. ffrench-Mullen, J.M.H., Koller, K., Zaczek, R., Coyle, J.T., Hori, N. and Carpenter, D.O. N-acetylaspartylglutamate: Possible role as the neurotransmitter of the lateral olfactory tract. *Proc. Nat. Acad. Sci.*, 82:3897-3900, 1985.
89. Greene, R.W. and Carpenter, D.O. Actions of neurotransmitters on pontine medial reticular formation neurons of the cat. *J. Neurophysiol.*, 54:520-531, 1985.
90. Hori, N., ffrench-Mullen, J.M.H. and Carpenter, D.O. Kainic acid responses and toxicity show pronounced  $\text{Ca}^{2+}$  dependence. *Brain Res.*, 358:380-384, 1985.
91. Gaillard, W.D. and Carpenter, D.O. Spectra of neurotransmitter receptors and ionic responses on cerebral A and B neurons in *Aplysia californica*. *Brain Res.*, 373:303-310, 1986.
92. Gaillard, W.D. and Carpenter, D.O. On the transmitter at the A-to-B cell in *Aplysia californica*. *Brain Res.*, 373:311-315, 1986.
93. ffrench-Mullen, J.M.H., Hori, N. and Carpenter, D.O. A comparison on the effects of quinolinate and N-methyl-aspartate on neurons in rat piriform cortex. *Neurosci. Lett.*, 63:66-70, 1986.
94. ffrench-Mullen, J.M.H., Hori, N. and Carpenter, D.O. Receptors for the excitatory amino acids on neurons in rat pyriform cortex. *J. Neurophysiol.*, 55:1283-1294, 1986.
95. Slater, N.T., David, J.A. and Carpenter, D.O. Relaxation studies on the interaction of hexamethonium with acetylcholine-receptor channels in *Aplysia* neurons. *Cell. Molec. Neurobiol.*, 6:191-211, 1986.
96. Leung, M.K., S.-Rozsa, K., Hall, A., Kuruvilla, S., Stefano, G.B. and Carpenter, D.O. Enkephalin-like substance in *Aplysia* nervous tissue and actions of leu-enkephalin on single neurons. *Life Sci.*, 38:1529-34, 1986.
97. Slater, N.T., Filbert, M. and Carpenter, D.O. Multiple interactions of anticholinesterases with *Aplysia* acetylcholine responses. *Brain Res.*, 375:407-412, 1986.
98. Carpenter, D.O. and Briggs, D.B. Insulin excites neurons of the area postrema and causes emesis. *Neurosci. Lett.*, 68:85-89, 1986.
99. Carpenter, D.O., Briggs, D.B., Knox, A.P. and Strominger, N.L. Radiation-induced emesis in the dog: Effects of lesions and drugs. *Rad. Res.*, 108:307-316, 1986.
100. Briggs, D.B. and Carpenter, D.O. Excitation of neurons in the canine area postrema by prostaglandins. *Cell. Molec. Neurobiol.*, 6:421-426, 1986.
101. Chesnut, T.J., Carpenter, D.O. and Strichartz, G.R. Three effects of venom from *conus striatus* on the delayed rectifier potassium current of molluscan neurons. *Toxicon*, 25:267-278, 1987.
102. Yakushiji, T., Tokutomi, N., Akaike, N. and Carpenter, D.O. Agonists of GABA responses, studied using internally perfused frog dorsal root ganglion neurons. *Neuroscience* 22:1123-1133, 1987.
103. Akaike, N., Yakushiji, T., Tokutomi, N. and Carpenter, D.C. Multiple mechanisms of antagonism of GABA responses. *Cell. Molec. Neurobiol.*, 7:97-103, 1987.
104. Hori, N., Galeno, T. and Carpenter, D.O. Responses of pyriform cortex neurons to excitatory amino acids: Voltage dependence, conductance changes and effects of divalent cations. *Cell. Molec. Neurobiol.*, 7:73-90, 1987.



105. Oyama, Y., King, W.M. and Carpenter, D.O. Edrophonium-induced membrane current in single neurons physically isolated from *Aplysia californica*. *Brain Res.*, 438:95-100, 1988.
106. Jahan-Parwar, B., S.-Rozsa, K., Salanki, J., Evans, M.L. and Carpenter, D.O. *In vivo* labeling of serotonin containing neurons by 5,7-dihydroxytryptamine in *Aplysia*. *Brain Res.*, 426:173-178, 1987.
107. King, W.M. and Carpenter, D.O. Distinct GABA and glutamate receptors may share a common channel in *Aplysia* neurons. *Neurosci. Lett.*, 82:343-348, 1987.
108. Carpenter, D.O., Briggs, D.B., Knox, A.P. and Strominger, N. Excitation of area postrema neurons by transmitters, peptides and cyclic nucleotides. *J. Neurophysiol.*, 59:358-369, 1988.
109. Carpenter, D.O., Hall, A.F. and Rahmann, H. Exogenous gangliosides induce direct voltage and conductance changes on isolated neurons. *Cell. Molec. Neurobiol.*, 8:245-250, 1988.
110. Hori, N., Carpenter, D.O. and Katsuda, N. Effect of acetylcholine on the pyramidal cell in the rat piriform cortex *in vitro*. *Neurosciences*, 13:172-174, 1987 (in Japanese).
111. Hori, N. and Carpenter, D.O. Excitatory amino acid receptors in piriform cortex do not show receptor desensitization. *Brain Res.*, 457:350-354, 1988.
112. Allen, C.N., Brady, R., Swann, J., Hori, N. and Carpenter, D.O. N-methyl-D-aspartate (NMDA) receptors are inactivated by trypsin. *Brain Res.*, 458:147-150, 1988.
113. Oyama, Y., Akaike, N. and Carpenter, D.O. Strychnine decreases the voltage-dependent  $\text{Ca}^{2+}$  current of both *Aplysia* and frog ganglion neurons. *Cell. Molec. Neurobiol.*, 8:307-314, 1988.
114. Oyama, Y., King, W.M., Allen, C.N., Hori, N. and Carpenter, D.O. Characterization of an inward current elicited by edrophonium in physically isolated and internally perfused *Aplysia* neurons. *Brain Res.*, 463:124-132, 1988.
115. Hori, N., Akaike, N. and Carpenter, D.O. Piriform cortex brain slices: Techniques for isolation of synaptic inputs. *J. Neurosci. Methods*, 25:197-208, 1988.
116. Oyama, Y., Evans, M.L., Akaike, N. and Carpenter, D.O. Electrophysiological detection of acetylcholinesterase activity using concentration clamp on physically isolated *Aplysia* neurons. *Neuroscience Res.*, 6:174-180, 1988.
117. Tsuda, Y., Oyama, Y., Carpenter, D.O. and Akaike, N. Effects of  $\text{Ca}^{2+}$  on the transient outward current of single isolated *Helix* central neurones. *Brit. J. Pharmacol.*, 95:526-530, 1988.
118. Oyama, Y., Hori, N., Evans, M.L., Allen, C.N. and Carpenter, D.O. Electrophysiological estimation of the actions of acetylcholinesterase inhibitors on acetylcholine receptor and cholinesterase in physically isolated *Aplysia* neurones. *Brit. J. Pharmacol.*, 96:573-582, 1989.
119. King, W.M. and Carpenter, D.O. Voltage-clamp characterization of  $\text{Cl}^-$  conductance gated by GABA and L-glutamate in single neurons of *Aplysia*. *J. Neurophysiol.*, 61:892-899, 1989.
120. Evans, M.L. and Carpenter, D.O. Desensitization kinetics of a chloride acetylcholine response in *Aplysia*. *Brain Res.*, 495:309-318, 1989.
121. Salanki, J., Evans, M.L. and Carpenter, D.O. Desensitization kinetics of a  $\text{K}^+$  acetylcholine response in *Aplysia*. *Brain Res.*, 495:298-308, 1989.
122. Büsselberg, D., Evans, M.L., Rahmann, H. and Carpenter, D.O. Effects of exogenous ganglioside and cholesterol application on excitability of *Aplysia* neurons. *Membrane Biochemistry*, 8:19-26, 1989.

123. Carpenter, D. Neural mechanisms of emesis. Canad. J. Physiol. Pharmacol., 68:230-236, 1990.
124. Oyama, Y., Hori, N., Allen, C.N., and Carpenter, D.O. Influences of trypsin and collagenase on acetylcholine responses of physically-isolated single neurons of *Aplysia californica*. Cell. Molec. Neurobiol., 10:193-205, 1990.
125. Büsselberg, D., Evans, M.L., Rahmann, H., and Carpenter, D.O. Lead inhibits the voltage-activated calcium current of *Aplysia* neurons. Toxicol. Lett., 51:51-57, 1990.
126. Doi, N., Carpenter, D.O. and Hori, N. Differential effects of baclofen and GABA on rat piriform cortex pyramidal neurons *in vitro*. Cell. Molec. Neurobiol., 10: 559-564, 1991.
127. Büsselberg, D., Evans, M.L., Rahmann, H. and Carpenter, D.O.  $Zn^{2+}$  blocks the voltage activated calcium current of *Aplysia* neurons. Neurosci. Letts., 117:117-122, 1990.
128. Büsselberg, D., Carpenter, D.O., Sugita, M., Araki, S., Satake, M. and Rahmann, H. Effects of exogenous lipid application on excitability of *Aplysia* neurons. Biomed. Res., 11:77-86, 1990.
129. Evans, M.L., Kadan, M.J., Hartig, P.R. and Carpenter, D.O. Correlation of  $^{125}I$ -LSD autoradiographic labelling with serotonin voltage clamp responses in *Aplysia* neurones. Synapse, 8:22-29, 1991.
130. S.-Rozsa, K., Stefano, G., Salanki, J. and Carpenter, D.O. Characterization of responses to enkephalins and FMRFamide on B neurons of the cerebral ganglion of *Aplysia*. Comp. Biochem. Physiol., 99C:403-412, 1991.
131. Büsselberg, D., Evans, M.L., Rahmann, H. and Carpenter, D.O. Lead and zinc block a voltage activated calcium channel of *Aplysia* neurons. J. Neurophysiol., 65:786-795, 1991.
132. Hori, N., Doi, N., Miyahara, S., Shinoda, Y. and Carpenter, D.O. Appearance of NMDA receptors triggered by anoxia independent of voltage *in vivo* and *in vitro*. Exp. Neurol., 112:304-311, 1991.
133. Büsselberg, D., Evans, M.L., Rahmann, H. and Carpenter, D.O. Effects of inorganic and triethyl lead and inorganic mercury on the voltage activated calcium channel of *Aplysia* neurons. NeuroToxicology, 12:733-744, 1991.
134. Evans, M.L., Büsselberg, D. and Carpenter, D.O.  $Pb^{2+}$  blocks calcium currents of cultured dorsal root ganglion cells. Neurosci. Letts., 129:103-106, 1991.
135. Kemenes, G., S.-Rozsa, K., Stefano, G. and Carpenter, D.O. Distinct receptors for leu- and met-enkephalin on the metacerebral giant cell of *Aplysia*. Cell. Molec. Neurobiol., 12:107-119, 1992.
136. Ayrapetyan, S.N. and Carpenter, D.O. Very low concentrations of acetylcholine and GABA modulate transmitter responses. NeuroReport 2:563-565, 1991.
137. Carpenter, D.O. and Hori, N. Neurotransmitter and peptide receptors on medial vestibular nucleus neurons. Ann. NY Acad. Sci., 656:668-686, 1992.
138. Hernadi, L., S.-Rozsa, K., Jahan-Parwar, B. and Carpenter, D.O. A topography and ultrastructural characterization of *in vivo* 5,7-dihydroxytryptamine-labelled serotonin-containing neurons in the central nervous system of *Aplysia californica*. Cell. Molec. Neurobiol., 12:317-326, 1992.
139. Carpenter, D.O., Fejtl, M., Ayrapetyan, S., Szarowski, D. and Turner, J.N. Dynamic changes in neuronal volume resulting from osmotic and sodium transport manipulations. Acta Biologica Hungarica, 43:39-48, 1992.
140. Ayrapetyan, S.N. and Carpenter, D.O. On the modulating effect of ultralow transmitter concentrations on the functional activity of the neuron membrane. J. Evol. Biochem. Physiol., 27:110-116, 1991.

141. Büsselberg, D., Michael, D., Evans, M.L., Carpenter, D.O. and Haas, H.L. Zinc ( $Zn^{2+}$ ) blocks voltage gated calcium channels in cultured rat dorsal root ganglion cells. *Brain Res.*, 593:77-81, 1992.
142. Matthews, M.R., Parsons, P.J. and Carpenter, D.O. Solubility of lead as lead (II) chloride in HEPES-Ringer and artificial seawater (Ca-ASW) solutions. *NeuroToxicology*, 14:283-290, 1993.
143. Hori, N., Büsselberg, D., Matthews, R., Parsons, P.J. and Carpenter, D.O. Lead blocks LTP by an action not at NMDA receptors. *Exp. Neurol.*, 119: 192-197, 1993.
144. Büsselberg, D., Evans, M.L., Haas, H.L. and Carpenter, D.O. Blockade of mammalian and invertebrate calcium channels by lead. *NeuroToxicology*, 14:249-258, 1993.
145. Riepe, M., Hori, N., Ludolph, A.C., Carpenter, D.O., Spencer, P.S. and Allen, C.N. Inhibition of energy metabolism by 3-nitropropionic acid activates ATP-sensitive potassium channels. *Brain Res.*, 586:61-66, 1992.
146. Hori, N., Hirotsu, I., Davis, P.J. and Carpenter, D.O. Long-term potentiation is lost in aged rats but preserved by calorie restriction. *NeuroReport*, 3:1085-1088, 1992.
147. Knox, A.P., Strominger, N.L., Battles, A.H. and Carpenter, D.O. Behavioral studies of emetic sensitivity in the ferret. *Brain Res. Bull.*, 31:477-484, 1993.
148. Allen, C.N., Spencer, P.S. and Carpenter, D.O.  $\beta$ -N-methylamino-L-alanine in the presence of bicarbonate is an agonist at non-N-methyl-D-aspartate-type receptors. *Neuroscience* 54:567-574, 1993.
149. Elekes, K., Stefano, G.B. and Carpenter, D.O. Enkephalin-like immunoreactive neurons in the central nervous system of gastropods (*Helix pomatia*, *Lymnaea stagnalis*, *Aplysia californica*): A comparative immunocytochemical study. *Cell Tiss. Res.* 272:329-41, 1993.
150. Büsselberg, D., Platt, B., Haas, H.L. and Carpenter, D.O. Voltage gated calcium channel currents of rat dorsal root ganglion (DRG) cells are blocked by  $Al^{3+}$ . *Brain Res.* 622:163-168, 1993.
151. Strominger, N.L., Knox, A.P. and Carpenter, D.O. The connectivity of the area postrema in the ferret. *Brain Res. Bull.*, 33:33-47, 1994.
152. Knox, A.P., Strominger, N.L., Battles, A.H. and Carpenter, D.O. The central connections of the vagus nerve in the ferret. *Brain Res. Bull.*, 33:49-63, 1994.
153. Lin, Y. and Carpenter, D.O. Medial vestibular neurons are endogenous pacemakers whose discharge is modulated by neurotransmitters. *Cell Molec. Neurobiol.*, 13:601-613, 1993.
154. Kemenes, G., S.-Rózsa, K. and Carpenter, D.O. Cyclic-AMP-mediated excitatory responses to leucine enkephalin in *Aplysia* neurones. *J. Exp. Biol.* 181: 321-328, 1993.
155. Büsselberg, D., Platt, B., Michael, D., Carpenter, D.O. and Haas, H.L. Mammalian voltage-activated calcium channel currents are blocked by  $Pb^{2+}$ ,  $Zn^{2+}$  and  $Al^{3+}$ . *J. Neurophysiol.*, 71:1491-1497, 1994.
156. Hori, N. and Carpenter, D.O. Transient ischemia causes a reduction of  $Mg^{2+}$  blockade of NMDA receptors. *Neurosci. Letts.*, 173:75-78, 1994.
157. Riepe, M.W., Hori, N., Ludolph, A.C. and Carpenter, D.O. Failure of neuronal ion exchange, not potentiated excitation, causes excitotoxicity after inhibition of oxidative phosphorylation. *Neuroscience*, 64:91-97, 1995.
158. Hori, N. and Carpenter, D.O. Functional and morphological changes induced by transient *in vivo* ischemia. *Exp. Neurol.*, 129:279-289, 1994.
159. Lin, Y. and Carpenter, D.O. Direct excitatory opiate effects mediated by non-synaptic actions on rat medial vestibular neurons. *Eur. J. Pharmacol.*, 262:99-106, 1994.

160. Carpenter, D.O. Epidemiological evidence for an association between exposure to 50 and 60 Hz magnetic fields and cancer. James Bay Publication Series, Hydro-Electric Development: Environmental Impacts - Paper No. 6, pp. 2-31, 1994.
161. Carpenter, D.O. Communicating with the public on issues of science and public health. Environ. Health Perspect. 103:127-130, 1995.
162. Fejtl, M., Gyori, J. and Carpenter, D.O.  $Hg^{2+}$  increases the open probability of carbachol-activated  $Cl^-$  channels in *Aplysia* neurons. NeuroReport, 5:2317-2320, 1994.
163. Carpenter, D.O. The public health significance of metal neurotoxicity. Cell Molec. Neurobiol., 14:591-597, 1994.
164. Gyori, J., Fejtl, M. and Carpenter, D.O. Effect of  $HgCl_2$  on acetylcholine, carbachol and glutamate currents of *Aplysia* neurons. Cell Molec. Neurobiol., 14:653-664, 1994.
165. Fejtl, M., Gyori, J. and Carpenter, D.O. Mercuric (II) chloride modulates single channel properties of carbachol activated  $Cl^-$  channels in cultured neurons of *Aplysia californica*. Cell Molec. Neurobiol., 14:665-674, 1994.
166. Carpenter, D.O., Matthews, M.R., Parsons, P.J. and Hori, N. Long-term potentiation in piriform cortex is blocked by lead. Cell Molec. Neurobiol., 14:723-733, 1994.
167. Salanki, J., Gyori, J. and Carpenter, D.O. Action of lead on glutamate-activated chloride currents in *Helix Pomatia L.* neurons. Cell Molec. Neurobiol., 14:755-768, 1994.
168. Carpenter, D.O. How hazardous wastes affect human health. Cent. Eur. J. Publ. Hlth. 2:6-9, 1994.
169. Oyama, Y., Carpenter, D.O., Ueno, S., Hayashi, H. and Tomiyoshi, F. Methylmercury induces  $Ca^{2+}$ -dependent hyperpolarization of mouse thymocytes: A flow-cytometric study using fluorescent dyes. Eur. J. Pharmacol., 293:101-107, 1995.
170. Fejtl, M., Szarowski, D.H., Decker, D., Buttle, K., Carpenter, D.O. and Turner, J.N. Three-dimensional imaging and electrophysiology of live *Aplysia* neurons during volume perturbation: confocal light and high-voltage electron microscopy. JMSA 1(2):75-85, 1995.
171. Carpenter, D.O., Kemenes, G., Elekes, K., Leung, M., Stefano, G., S.-Rozsa, K. and Salanki, J. Opioid peptides in the nervous system of *Aplysia*: A combined biochemical immunocytochemical, and electrophysiological study. Cell Molec. Neurobiol. 15:239-256, 1995.
172. Riepe, M. and Carpenter, D.O. Delayed increase of cell volume of single pyramidal cells in live hippocampal slices upon kainate application. Neurosci. Letts. 191:35-38, 1995.
173. Son, H. And Carpenter, D.O. Protein kinase C activation is necessary but not sufficient for induction of LTP at the synapse of mossy fiber-CA3 in the rat hippocampus. Neuroscience 72:1-13, 1996.
174. Iwase, T., Hori, N., Morioka, T. and Carpenter, D.O. Low power laser irradiation reduces ischemic damage in hippocampal slices *in vitro*. Lasers Surg. Med., 19:465-450, 1996.
175. Carpenter, D.O., King, W.M. and McCreery, M.J. The role of glutamate reuptake in regulation of glutamate responses in *Aplysia* neurons. Acta Biologica Hungaria 46:363-373, 1995.
176. Saghian, A.A., Ayrapetyan, S.N. and Carpenter, D.O. Low concentrations of ouabain stimulate Na/Ca exchange in neurons. Cell Molec. Neurobiol., 16:489-498, 1996.
177. Platt, B., Carpenter, D.O., Büsselberg, D., Reymann, K.G. and Riedel, G. Aluminum impairs hippocampal long-term potentiation in rats *in vitro* and *in vivo*. Exp. Neurol., 134:73-86, 1995.

178. Rubakhin, S.S., Gyori, J., Carpenter, D.O. and Salanki, J. HgCl<sub>2</sub> potentiates GABA activated currents in *Lymnaea stagnalis* L. neurons. *Acta Biologica Hungaria*, 46:431-444, 1995.
  179. Fejtl, M. and Carpenter, D.O. Neurite outgrowth is enhanced by conditioning factor(s) released from central ganglia of *Aplysia californica*. *Neurosci. Letts.*, 199:33-36, 1995.
  180. Riepe, M.W., Niemi, W.N., Megow, D., Ludolph, A.C. and Carpenter, D.O. Mitochondrial oxidation in rat hippocampus can be preconditioned by selective chemical inhibition of SDH. *Exp. Neurol.*, 138:15-21, 1996.
  181. Son, H. and Carpenter, D.O. Interactions among paired-pulse facilitation and post-tetanic and long-term potentiation in the mossy fiber-CA3 pathway in rat hippocampus. *Synapse*, 23:302-311, 1996.
  182. Carpenter, D.O., Suk, W.A., Blaha, K. and Cikrt, M. Hazardous wastes in Eastern and Central Europe. *Environ. Health Perspect.*, 104:244-248, 1996.
  183. Son, H., Davis, P.J. and Carpenter, D.O. Time course and involvement of protein kinase C-mediated phosphorylation of F1/GAP-43 in area CA3 after the mossy fiber stimulation. *Cell. Molec. Neurobiol.*, 17:171-194, 1997.
  184. Dyatlov, V.A., Platoshin, A.V., Lawrence, D.A. and Carpenter, D.O. Mercury (Hg<sup>2+</sup>) enhances the depressant effect of kainate on Ca-inactivated potassium current in telencephalic cells derived from chick embryos. *Toxicol. Appl. Pharmacol.*, 138:285-297, 1996.
  185. Carpenter, D.O. and Conway, J.B. Optimizing professional education in public health. *J. Public Health Management Practice*, 2:66-72, 1996.
  186. Carpenter, D.O. Great Lakes contaminants: A shift in human health outcomes. *Health and Environment Digest*, 10:17-19, 1996.
  187. Boldyrev, A.A., Stvolinsky, S.L., Tyulina, O.V., Koshelev, V.B., Hori, N. and Carpenter, D.O. Biochemical and physiological evidence that carnosine is an endogenous neuroprotector against free radicals. *Cell. Molec. Neurobiol.*, 17:259-271, 1997.
  188. Szücs, A., Angiello, C., Salánki, J. and Carpenter, D.O. Effects of inorganic mercury and methylmercury on the ionic currents of cultured rat hippocampal neurons. *Cell. Molec. Neurobiol.*, 17:273-288, 1997.
  189. Niemi, W.D., Slivinski, K., Audi, J., Rej, R. and Carpenter, D.O. Propylthiouracil treatment reduces long-term potentiation in area CA1 of neonatal rat hippocampus. *Neurosci. Letts.*, 210:127-129, 1996.
  190. Son, H., Madelian, V. and Carpenter, D.O. The translocation and involvement of protein kinase C in mossy fiber-CA3 long-term potentiation in hippocampus of the rat brain. *Brain Res.*, 739:282-292, 1997.
  191. Oyama, Y., Carpenter, D.O., Chikahisa, L. and Okazaki, E. Flow-cytometric estimation on glutamate- and kainate-induced increases in intracellular Ca<sup>2+</sup> of brain neurons. *Brain Research*, 728:121-124, 1996.
  192. Carpenter, D.O., Stoner, C.R.T. and Lawrence, D.A. Flow cytometric measurements of neuronal death triggered by PCBs. *NeuroToxicology*, 18:507-514, 1997.
  193. Azatian, K.V., Ayrapetyan, S.N. and Carpenter, D.O. Metabotropic GABA receptors regulate acetylcholine responses on snail neurons. *Gen. Pharmacol.*, 29:67-72, 1997.
- Carpenter, D.O., Stoner, C.T., Lawrence, D.A., Niemi, W.D., Shain, W. and Seegal, R. Multiple mechanisms of PCB neurotoxicity. Proceedings of the 1996 Pacific Basin Conference on Hazardous Waste, Kuala Lumpur, Malaysia, CONF-9611157, pp. 404-918.

- Carpenter, D.O. New Dimensions in our understanding of the human health effects of environmental pollutants. Proceedings of the 1996 Pacific Basin Conference on Hazardous Waste, Kuala Lumpur, Malaysia, CONF-9611157, pp. 37-53.
196. Carpenter, D.O. Possible effects of electromagnetic fields on the nervous system and development. Men. Retard. Dev. Dis. Res. Rev. 3:270-274, 1997.
  197. Chiarenzelli, J., Scrudato, R., Bush, B., Carpenter, D. and Bushart, S. Do large-scale remedial and dredging events have the potential to release significant amounts of semi-volatile compounds to the atmosphere? Environ. Hlth. Perspect., 106:47-49, 1998.
  198. Dyatlov, V.A., Dytlova O.M., Parsons, P.H., Lawrence, D.A. and Carpenter, D.O. Lipopolysaccharide and interleukin-6 enhance lead entry into cerebellar neurons: Application of a new and sensitive flow cytometric technique to measure intracellular lead and calcium concentrations. NeuroToxicology, 19:293-302, 1998.
  199. Dyatlov, V.A., Platoshin, A.V., Lawrence, D.A. and Carpenter, D.O. Lead potentiates cytokine- and glutamate-mediated increases in permeability of the blood-brain barrier. NeuroToxicology, 19:283-292, 1998.
  200. Niemi, W.D., Audi, J., Bush, B. and Carpenter, D.O. PCBs reduce long-term potentiation in the CA1 region of rat hippocampus. Exper. Neurol., 151:26-34, 1998.
  201. Carpenter, D.O. Health effects of metals. Cent. Eur. J. Publ. Hlth., 6:160-163, 1998.
  202. Carpenter, D.O., Bláha, K., Buekens, A., Cikrt, M., Damstra, T., Dellinger, B., Sarofim, A., Suk, W.A., Wyes, H. and Zejda, J. Remediation of hazardous wastes in Central and Eastern Europe: Technology and health effects. Cent. Eur. J. Publ. Hlth., 6:77-78, 1998.
  203. Carpenter, D.O. Human health effects of environmental pollutants: New Insights. Environ. Monitor. Assess. J., 53:245-258, 1998.
  204. Dyatlov, V.A., Makovetskaia, V.V., Leonhardt, R., Lawrence, D.A. and Carpenter, D.O. Vitamin E enhances  $\text{Ca}^{2+}$ -mediated vulnerability of immature cerebellar granule cells to ischemia. Free Rad. Biol. Med., 25: 793-802, 1998.
  205. Fitzgerald, E.F., Schell, L.M., Marshall, E.G., Carpenter, D.O., Suk, W.A. and Zejda, J.E. Environmental pollution and child health in Central and Eastern Europe. Environ. Health Persp., 106:307-311, 1998.
  206. Carpenter, D.O., Arcaro, K.F., Bush, B., Niemi, W.D., Pang, S. and Vakharia, D.D. Human health and chemical mixtures: An overview. Environ. Health Perspect., 106: 1263-1270, 1998.
  207. Carpenter, D.O., Cikrt, M. and Suk, W.A. Hazardous wastes in Eastern and Central Europe: Technology and health effects. Environ. Health Perspect., 107: 3-4, 1999.
  194. Carpenter, D.O. Polychlorinated biphenyls and human health. Int. J. Occup. Med. Environ. Hlth. 11: 291-303, 1998.
  195. Boldyrev, A.A., Johnson, P., Yanzhang, W., Tan, Y. and Carpenter, D.O. Carnosine and taurine protect rat cerebellar granular cells from free radical damage. Neurosci. Letts., 263: 169-172, 1999.
  196. Boldyrev, A.A., Carpenter, D.O., Huentelman, M.J., Peters, C.M. and Johnson, P. Sources of reactive oxygen species production in excitotoxin-stimulated neurons. Biophys. Biochem. Res. Commun., 256: 320-324, 1999.
  197. Ayrapetyan, S.N., Ayrapetyan, G. and Carpenter, D.O. The electrogenic sodium pump activity in *Aplysia* neurons is not potential dependent. Acta Biologica Hungarica, 50: 27-34, 1999.

198. Boldyrev, A., Song, R., Lawrence, D. and Carpenter, D.O. Carnosine protects against excitotoxic cell death independently of effects on reactive oxygen species. Neuroscience, 94: 571-577, 1999.
199. Boldyrev, A., Song, R., Dyatlov, V.A., Lawrence, D.A. and Carpenter, D.O. Neuronal cell death and reactive oxygen species. Cell Molec. Neurobiol., 20:433-450, 2000.
200. Gyori, J., Platoshyn, O., Carpenter, D.O. and Salanki, J. Effect of inorganic- and organic tin compounds on ACh- and voltage-activated Na currents. Cell Molec. Neurobiol. 20:591-604, 2000.
215. Hussain, R.J., Gyori, J., DeCaprio, A.P. and Carpenter, D.O. *In vivo* and *in vitro* exposure to PCB 153 reduces long-term potentiation. Environ. Hlth. Perspect., 108 :827-831, 2000.
216. Negoita, S., Swamp, L., Kelley, B. and Carpenter, D.O. Chronic diseases surveillance of St. Regis Mohawk health service patients. J. Public Health Management Practice, 7:84-91, 2001.
217. Hussain, R.J., Parsons, P.J., Carpenter, D.O. Effects of lead on long-term potentiation in hippocampal CA3 vary with age. Dev. Brain Res., 121: 243-252, 2000.
218. Tanji, M., Katz, B.H., Spink, B.C. and Carpenter, D.O. Growth inhibition of MCF-7 cells by estrogen is dependent upon a serum factor. Anticancer Res., 20: 2779-2784, 2000.
219. Tanji, M. and Carpenter, D.O. A steroid-binding protein mediates estrogen-dependent inhibition of growth of MCF-7 breast cancer cells. Anticancer Res., 20:2785-2790, 2000.
220. Gyori, J., Hussain, R., Carpenter, D.O. Long-term potentiation in CA1 region of rat brain slices is blocked by PCB 153. Cent. Europ. J. Publ. Hlth., 8: 21-22, 2000.
221. Carpenter, D.O. Human health effects of polychlorinated biphenyls. Cent. Eur. J. Public Health, 8: 23-24, 2000.
- 221a. Sukdolova, V., Negoita, S., Hubicki, L., DeCaprio, A., and Carpenter, D.O. The assessment of risk to acquired hypothyroidism from exposure to PCBs: a study among Akwesasne Mohawk women. Cent. Eur. J. Public Health, 8: 167-168, 2000.
222. Carpenter, D.O., Chew, F.T., Damstra, T., Lam, L.H., Landrigan, P.J., Makalinao, I., Peralta, G.L. and Suk, W.A. Environmental threats to the health of children: The Asian perspective. Environ. Hlth. Perspect., 108: 989-992, 2000.
223. Boldyrev, A.A., Carpenter, D.O. and Johnson, P. Natural mechanisms of protection of neurons against oxidative stress. Recent Res. Devel. Comparative Biochem. & Physiol. 1: 91-103, 2000.
224. Strominger, N.L., Hori, N., Carpenter, D.O., Tan, Y. and Folger W.H. Effects of acetylcholine and GABA on neurons in the area postrema of *Suncus murinus* brainstem slices. Neurosci. Letts. 309: 77-80, 2001.
225. Strominger, N.L., Brady, R., Gullikson, G. and Carpenter, D.O. Imiquimod-elicited emesis is mediated by the area postrema, but not by direct neuronal activation. Brain Res. Bull. 55: 445-451, 2001.
226. Hori, N., Tan, Y., Strominger, N.L. and Carpenter, D.O. Intracellular activity of rat spinal cord motoneurons in slices. J. Neurosci. Meth. 112: 185-191, 2001.
227. Sukocheva, O.A., Abramov, A.Y., Levitskaya, J.O., Gagelgans, A.I. and Carpenter, D.O. Modulation of intracellular Ca concentration by vitamin B12 in rat thymocytes. Blood Cells. Mol. Dis. 27: 812-824, 2001.
228. Gilbertson, M., Carpenter, D. and Upshur, R. Methodology for assessing community health in Areas of Concern: Measuring the adverse effects on human health. Environ. Health Perspect. 109 (Suppl 6): 811-812, 2001.

229. Carpenter, D.O., Shen, Y., Nguyen, T., Le, L. and Lininger, L.L. Incidence of endocrine disease among residents of New York Areas of Concern. Environ. Health Perspect. 109: (Suppl 6) 845-851, 2001.
230. Suk, W.A., Carpenter, D.O., Cirk, M. and Smerhovsky, Z. Metals in Eastern and Central Europe: Health effects, sources of contamination and methods of remediation. Internat. J. Occup. Med. Environ. Health 14, 151-156, 2001.
231. Carpenter, D.O. Effects of metals on the nervous system of humans and animals. Internat. J. Occup. Med. Environ. Health 14: 209-218, 2001.
232. Carpenter, D.O., Arcaro, K. and Spink, D.C. Understanding the human health effects of chemical mixtures. Environ. Health Perspect. 110 (Suppl 1), 25-42, 2002.
233. Carpenter, D.O., Nguyen, T., Le, L., Kudyakov, R. and Lininger, L. Human disease in relation to residence near hazardous waste sites. Proceedings of The 10<sup>th</sup> Pacific Basin Conference on Hazardous Waste, Okayama, Japan, December 5-7, 2001.
234. Carpenter, D.O., Tarbell, A., Fitzgerald, E., Kadlec, M.J., O'Hehir, D.O. and Bush, B. University-community partnership for the study of environmental contamination at Akwesasne. In: Biomarkers of Environmentally Associated Disease, S.H. Wilson and W.A. Suk, editors, CRC Press/Lewis Publishers, 507-523, 2002.
235. Carpenter, D.O., Hussain, R.J., Berger, D.F., Lombardo, J.P., Park, H-Y. Electrophysiological and behavioral effects of perinatal and acute exposure of rats to lead and polychlorinated biphenyls. Environ. Health Perspect., 110: 377-386, 2002.
236. Hori, N., Tan, Y., King, M., Strominger, N.L. and Carpenter, D.O. Differential actions and excitotoxicity of glutamate agonists on motoneurons in adult mouse cervical spinal cord slices. Brain Res., 958: 434-438, 2002.
237. Laemle, L.K., Hori, N., Strominger, N.L., Tan, Y. and Carpenter, D.O. Physiological and anatomical properties of the suprachiasmatic nucleus of an anophthalmic mouse. Brain Res., 953: 73-81, 2002.
238. Hori, N., Tan, Y., Strominger, N.L. and Carpenter, D.O. Rat motoneuron cell death in development correlates with loss of N-methyl-D-aspartate receptors. Neurosci. Letts., 330:131-134, 2002.
239. Carpenter, D.O., Morris, D.L. and Legator, M. Initial attempts to profile health effects with types of exposure in Anniston, Alabama. EEB, 12: 191-195, 2003.
240. Carpenter, D.O., Nguyen, T., Le, L., Baibergenova, A. and Kudyakov, R. Profile of health effects related to proximity to PCB-contaminated hazardous waste sites in New York. EEB, 12: 173-180, 2003.
241. Hori, N., Carp, J.S., Carpenter, D.O. and Akaike, N. Corticospinal transmission to motoneurons in cervical spinal slices from adult rats. Life Sci., 72: 389-396, 2002.
242. Carpenter, D.O. and Hussain, R.J. Cell-to-cell communication of neurons is impaired by metals. Mat.-wiss. U. Werkstofftech. 34: 1-8, 2003.
243. Tan, Y., Hori, N. and Carpenter, D.O. The mechanism of presynaptic long-lasting-depression mediated by group 1 metabotropic glutamate receptors. Cell. Molec. Neurobiol., 23: 187-203, 2003.
244. Baibergenova, A., Kudyakov, R., Zdeb, M., and Carpenter, D.O. Low birth weight and residential proximity to PCB-contaminated waste sites. Environ. Health Perspect., 111: 1352-1357, 2003.
245. Nishizaki, Y., Oyama, Y., Sakai, Y., Hiramata, S., Tomita, K., Nakao, H., Umebayashi, C., Ishida, S., Okano, Y. and Carpenter, D.O. PbCl<sub>2</sub>-induced hyperpolarization of rat



- thymocytes: Involvement of charybdotoxin-sensitive K<sup>+</sup> channels. *Environ. Toxicol.*, 18(5): 321-326, 2003.
246. Hussain, R.J. and Carpenter, D.O. The effects of protein kinase C activity on synaptic transmission in two areas of rat hippocampus. *Brain Res.*, 990: 28-37, 2003.
  247. Suk, W.A., Ruchirawat, K., Balakrishnan, K., Berger, M., Carpenter, D., Damstra, T., Pronczuk de Garbino, J., Koh, D., Landrigan, P.J., Makalinao, I., Sly, P.D., Xu, Y. and Zheng, B.S. Environmental threats to children's health in Southeast Asia and the Western Pacific. *Environ. Health Perspect.* 111: 1340, 2003.
  248. Carpenter, D.O. The need for global environmental health policy. *New Solutions*, 13(1): 53-59, 2003.
  249. Tan, Y., Li, D., Song, R., Lawrence, D. and Carpenter, D.O. Ortho-substituted PCBs kill thymocytes. *Toxicol. Sci.*, 76: 328-337, 2003.
  250. Boldyrev, A., Bulygina, E., Carpenter, D.O. and Schoner, W. Glutamate receptors communicate with Na<sup>+</sup>/K<sup>+</sup>-ATPase in rat cerebellum granule cells: Demonstration of differences in the action of several metabotropic and ionotropic glutamate agonists on intracellular reactive oxygen species and the sodium pump. *J. Molec. Neurosci.*, 21:213-222, 2003.
  251. Hites, R.A., Foran, J.A., Carpenter, D.O., Hamilton, M.C., Knuth, B.A. and Schwager, S.J. Global assessment of organic contaminants in farmed salmon. *Science* 303: 226-229, 2004.
  252. Sandal, S., Yilmaz, B., Chen, C-H and Carpenter, D.O. Comparative effects of technical toxaphene, 2,5-dichloro-3-biphenylol and octabromodiphenylether on cell viability, [Ca<sup>2+</sup>]<sub>i</sub> levels and membrane fluidity in mouse thymocytes. *Toxicol. Letts.*, 151: 417-428, 2004.
  253. Tan, Y., Chen, C-H., Lawrence, D. and Carpenter, D.O. Ortho-substituted PCBs kill cells by altering membrane structure. *Toxicol. Sci.*, 80: 54-59, 2004.
  254. Tan, Y., Song, R., Lawrence, D. and Carpenter, D.O. Ortho-substituted but not coplanar PCBs rapidly kill cerebellular granule cells. *Toxicol. Sci.*, 79: 147-156, 2004.
  255. Ozcan, M., Yilmaz, B., King, W.M. and Carpenter, D.O. Hippocampal long-term potentiation (LTP) is reduced by a coplanar PCB congener. *NeuroToxicology*, 25: 981-988, 2004.
  256. Ssempebwa, J.C., Carpenter, D.O., Yilmaz, B., DeCaprio, A.P., O'Hehir, D.J. and Arcaro, K.F. Waste crankcase oil: an environmental contaminant with potential to modulate estrogenic responses. *J. Toxicol. Environ. Hlth, Part A*, 67: 1081-1094, 2004.
  257. Foran, J.A., Hites, R.A., Carpenter, D.O., Hamilton, M.C., Mathews-Amos, A. and Schwager, S.J. A survey of metals in tissues of farmed Atlantic and wild Pacific salmon. *Environ. Toxicol. Chem.*, 23: 2108-2110, 2004.
  258. Oenga, G.N., Spink, D.C. and Carpenter, D.O. TCDD and PCBs inhibit breast cancer cell proliferation in vitro. *Toxicol. In Vitro*, 18: 811-819, 2004.
  259. Hussain, R.J. and Carpenter, D.O. A comparison of the roles of protein kinase C in long-term potentiation in rat hippocampal areas CA1 and CA3. *Cell. Molec. Neurobiol.*, 25: 649-661, 2005.
  260. Hites, R.A., Foran, J.A., Schwager, S.J., Knuth, B.A., Hamilton, M.C. and Carpenter, D.O. Global assessment of polybrominated diphenyl ethers in farmed and wild salmon. *Organohalogen Compounds*, 66: 3826-3829, 2004.

261. Kudyakov, R., Baibergenova, A., Zdeb, M. and Carpenter, D.O. Respiratory disease in relation to patient residence near to hazardous waste sites. Environ. Toxicol. Pharmacol., 18: 249-257, 2004.
262. Gilbertson, M. and Carpenter, D.O. An ecosystem approach to the health effects of mercury in the Great Lakes basin ecosystem. Environ. Res. 95: 240-246, 2004.
263. Hites, R.A., Foran, J.A., Schwager, S.J., Knuth, B.A., Hamilton, M.C. and Carpenter, D.O. Global assessment of polybrominated diphenyl ethers in farmed and wild salmon. Environ. Sci. Technol., 38: 4945-4949, 2004.
264. DeCaprio, A.P., Johnson, G.W., Tarbell, A.M., Carpenter, D.O. Chiarenzelli, J.R., Morse, G.S., Santiago-Rivera, A.L., Schymura, M.J., and the Akwesasne Task Force on the Environment. PCB exposure assessment by multivariate statistical analysis of serum congener profiles in an adult Native American population. Environ. Res., 98: 284-302, 2005.
265. Boldyrev, A.A., Kazey, V.I., Leinsoo, T.A., Mashkina, A.P., Tyulina O.V., Tuneva, J.O., Chittur, S. and Carpenter, D.O. Rodent lymphocytes express functionally active glutamate receptors. Biochem. Biophys. Res. Comm., 324: 133-139, 2004.
266. Boldyrev, A.A., Koudinov, A., Berezov, T. and Carpenter, D.O. Amyloid- $\beta$  induced cell death is independent of free radicals. J. Alzheimer's Dis., 6: 633-638, 2004.
267. Neagu, B., Strominger, N.L. and Carpenter, D.O. Use of bipolar parallel electrodes for well-controlled microstimulation in a mouse hippocampal brain slice. J. Neurosci. Meth., 144: 153-163, 2005.
268. Suk, W.A., Avakian, M.D., Carpenter, D., Groopman, J.D., Scammell, M. and Wild, C.P. Human exposure monitoring and evaluation in the Arctic: The importance of understanding exposures to the development of public health policy. Environ. Health Perspect. 112: 113-120, 2004.
269. Neagu, B., Neagu, E.R., Strominger, N.L. and Carpenter, D.O. A new fast electrophysiological response measured extracellularly in a mouse hippocampal brain slice. Neurosci. Letts., 381: 179-184, 2005.
270. Sergeev, A.V. and Carpenter, D.O. Hospitalization rates for coronary heart disease in relation to residence near areas contaminated with POPs and other pollutants. Environ. Health Perspect., 113: 756-761, 2005.
271. Foran, J.A., Carpenter, D.O., Hamilton, M.C., Knuth, B.A. and Schwager, S.J. Risk-based consumption advice for farmed Atlantic and wild Pacific salmon contaminated with dioxins and dioxin-like compounds. Environ. Health Perspect. 113: 552-556, 2005.
272. Shaw, S.D., Bourakovsky, A., Brenner, D., Carpenter, D.O., Tao, L., Kannan, K. and Hong, C-S. Polybrominated diphenyl ethers (PBDEs) in farmed salmon from Maine and Eastern Canada. In: Proceedings of 25<sup>th</sup> International Symposium on Halogenated Environmental Organic Pollutants and POPs (DIOXIN 2005), August 21-26, 2005, Toronto, Canada.
273. Carpenter, D.O., DeCaprio, A.P., O=Hehir, D., Akhtar, F., Johnson, G., Scrudato, R.J., Apatiki, L., Kava, J., Gologergen, J., Miller, P.K. and Eckstein, L. Polychlorinated biphenyls in serum of the Siberian Yupik people from St. Lawrence Island, Alaska. Int. J. Circumpolar Health, 64(4): 322-335, 2005.
274. Foran, J.A., Good, D.H., Carpenter, D.O., Hamilton, M.C., Knuth, B.A. and Schwager, S.J. Quantitative analysis of the benefits and risks of consuming farmed and wild salmon. J. Nutr 135: 2639-2643, 2005.

275. Huang, X., Hites, R.A., Foran, J.A., Hamilton, C., Knuth, B.A., Schwager, S.J. and Carpenter, D.O. Consumption advisories for salmon based on risk of cancer and non-cancer health effects. *Environ. Res.*, 101: 263-274, 2006.
276. Shcherbatykh, I., Huang, X., Lessner, L. and Carpenter, D.O. Hazardous waste sites and stroke in New York State. *Environ. Health*, 4:18, 2005.
277. Hamilton, M.C., Hites, R.A., Schwager, S.J., Foran, J.A., Knuth, B.A. and Carpenter, D.O. Lipid composition and contaminants in farmed and wild salmon. *Environ. Sci. Tech.*, 39: 8622-8629, 2005.
278. Yilmaz, B., Sandal, S., Chen, C-H. and Carpenter, D.O. Effects of PCB 52 and PCB 77 on cell viability,  $[Ca^{2+}]_i$  levels and membrane fluidity in mouse thymocytes. *Toxicology*, 217: 184-193, 2006.
279. Tan, Y., Hori, N., and Carpenter, D.O. Electrophysiological effects of three groups of glutamate metabotropic receptors in rat piriform cortex. *Cell. Molec. Neurobiol.*, 26: 915-924, 2006.
280. Boldyrev, A.A., Carpenter, D.O. and Johnson, P.A., Emerging evidence for a similar role of glutamate receptors in the nervous and immune systems. *J. Neurochem.*, 95: 913-918, 2005.
281. Sandal, S., Yilmaz, B., Godekmerdan, A., Kelestimur, H. and Carpenter, D.O. Effects of PCBs 52 and 77 on Th1/Th2 balance in mouse thymocyte cell cultures. *Immunopharmacol. Immunotoxicol.* 27: 601-613, 2005.
282. Carpenter, D.O. Environmental contaminants and learning and memory. *International Congress Series*, 1287: 185-189, 2006.
283. Carpenter, D.O. Polychlorinated biphenyls (PCBs): Routes of exposure and effects on human health. *Rev. Environ. Health*, 21: 1-23, 2006.
284. Huang, X., Lessner, L. and Carpenter, D.O. Exposure to persistent organic pollutants and hypertensive disease. *Environ. Res.*, 102: 101-106, 2006.
285. Carpenter, D.O., El-Qaderi, S., Fayzieva, D., Gilani, A., Hambartsumyan, A., Herz, K., Isobaev, M., Kasymov, O., Kudyakov, R., Majitova, Z., Mamadov, E., Nemer, L., Revich, B., Stege, P., Suk, W., Upshur, R., Yilmaz, B. and Zaineh K. Children's environmental health in Central Asia and the Middle East. *Int. J. Occup. Environ. Health*, 12: 362-368, 2006.
286. King, W.M., Sarup, V., Sauve, Y., Moreland, C.M., Carpenter, D.O. and Sharma, S.C. Expansion of visual receptive fields in experimental glaucoma. *Visual Neurosci.* 23: 137-142, 2006.
287. Tuneva, J., Chittur, S., Boldyrev, A.A., Birman, I. and Carpenter, D.O. Cerebellar granule cell death induced by aluminum. *Neurotox. Res.*, 9: 297-304, 2006.
288. Trasande, L., Boscarino, J., Graber, N., Falk, R., Schechter, C., Dunkel, G., Geslani, J., Moline, J., Kaplan-Liss, E., Miller, R.K., Korfmacher, K., Carpenter, D., Balk, S.J., Laraque, D., Frumkin, H. and Landrigan, P.J. The environment in pediatric practice: A study of New York pediatricians' attitudes, beliefs, and practices towards children's environmental health. *J. Urban Health*, 2006, DOI: 10.1007/s11524-006-9071-4.
289. Surdu, S., Montoya, L.D., Tarbell, A. and Carpenter, D.O. Childhood asthma and indoor allergens in Native Americans in New York. *Environ. Health: A Global Access Science Source*, 5:22, 2006. DOI: 10.1186/1476-069X-5-22.
290. Ozcan M., Yilmaz, B. and Carpenter, D.O. Effects of melatonin on synaptic transmission and long term potentiation in two areas of mouse hippocampus. *Brain Res.*, 1111: 90-94, 2006.

291. Shaw, S.D., Brenner, D., Berger, M.L., Pulser, E.L., Carpenter, D.O., Hong, C-W and Kannan K. PCBs, dioxin-like PCBs, dioxins, and organochlorine pesticides in farmed salmon (*Salmo salar*) from Maine and Eastern Canada. *Environ. Sci. Technol.* 40: 5347-5354, 2006.
292. Yilmaz, B., Ssempebwa J., Mackerer, C.R., Arcaro, K.F. and Carpenter, D.O. Effects of polycyclic aromatic hydrocarbon-containing oil mixtures on generation of reactive oxygen species and cell viability in MCF-7 breast cancer cells. *J. Toxicol. Environ. Health, Part A*: 70: 1-8, 2007.
293. Kouznetsova, M., Huang, X., Ma, J., Lessner, L. and Carpenter, D.O. Increased rate of hospitalization for diabetes and residential proximity of hazardous waste sites. *Environ. Health Perspect.*, 115:75-79, 2007.
294. Yilmaz, Y., Seyran, A.D., Sandal, S., Aydin, M., Colakoglu, N., Kocer, M. and Carpenter, D.O. Modulatory effects of Aroclors 1221 and 1254 on bone turnover and vertebral histology in intact and ovariectomized rats. *Toxicology Letts.*, 166: 276-294, 2006.
295. Shcherbatykh, I. and Carpenter, D.O. The role of metals in the etiology of Alzheimer's disease. *J. Alzheimer's Dis.*, 11: 191-205, 2007.
296. Surdu S, Neamtiu I, Gurzau E, Kasler I and Carpenter D. Blood lead levels and hand lead contamination in children ages 4-6 in Copsa Mica, Romania. In: *Environmental Health in Central and Eastern Europe*. KC Donnelly and LH Cizmas, Eds. Springer Netherlands. pp. 123-134, 2007.
297. Carpenter D.O. The importance of the Great Lakes Water Quality Agreement. *J. Public Health Policy* 28: 216-220, 2007.
298. Codru N, Schymura MJ, Negoita S, the Akwesasne Task Force on the Environment, Rej R and Carpenter DO. Diabetes in relation to serum levels of polychlorinated biphenyls (PCBs) and chlorinated pesticides in adult Native Americans. *Environ Health Perspect.* 115: 1442-1447, 2007.
299. Carpenter DO. Biomarcadores de efectos neuroconductuales. *Acta Toxicol Argent* 14 (Suplemento): 11-12, 2006.
300. Hennig B, Ormsbee L, Bachas L, Silverstone A, Milner J, Carpenter D, Thompson C and Suk WA. Introductory comments: nutrition, environmental toxins and implications in prevention and intervention of human diseases. *J. Nutr. Biochem* 189: 161-163, 2007.
301. Arnold R, Armour MA, Barich J, Cebrian M, Cifuentes L, Kirk D, Koh D, Lewis ND, Ling B, Makalinao I, Maiden T, Paz-y-Mino C, Peralta G, Singh K, Sly P, Suk W, Woodward A, Zheng B and Carpenter DO. Threats to human health and environmental sustainability in the Pacific Basin: The 11<sup>th</sup> International Conference of the Pacific Basin Consortium. *Environ Health Perspect.* 115: 1770-1775, 2007.
302. Parrish RR, Horstwood M, Arnason JG, Chenery S, Brewer T, Lloyd NS and Carpenter DO (2008) Depleted uranium contamination by inhalation exposure and its detection after approximately 25 years: Implications for health assessment. *Sci Total Environ* 390: 58-68.
303. Goncharov A, Haase RF, Santiago-Rivera A, Morse G, Akwesasne Task Force on the Environment, McCaffrey RJ, Rej R and Carpenter DO. (2008) High serum PCBs are associated with elevation of serum lipids and cardiovascular disease in a Native American population. *Environ Res.* 106: 226-239.
304. Ma J, Kouznetsova M, Lessner L and Carpenter DO. Asthma and infectious respiratory disease in children – correlation to residence near hazardous waste sites. *Paediatr Respir Rev* 8: 292-298, 2007.

305. Schell LM, Gallo MV, Denham M, Ravenscroft J, DeCaprio AP and Carpenter DO (2008) Relationship of thyroid hormone levels of polychlorinated biphenyls, lead, p,p'-DDE and other toxicants in Akwesasne Mohawk youth. *Environ Health Perspect.* 116: 806-813.
306. Ssempebwa J and Carpenter DO (2009) The generation, use and disposal of waste crankcase oil in developing countries: A case for Kampala District, Uganda. *J Hazard Materials* 161: 835-841.
307. Carpenter DO (2008) Environmental contaminants as risk factors for developing diabetes. *Rev Environ Health* 23: 59-74.
308. Shaw SD, Berger ML, Brenner D, Carpenter DO, Lao L, Hong CS and Kannan K (2008) Polybrominated diphenyl ethers (PBDEs) in farmed and wild salmon marketed in the Northeastern United States. *Chemosphere* 71: 1422-1431.
309. Sandel S, Yilmaz B and Carpenter DO (2008) Genotoxic effects of PCB 52 and PCB 77 on cultured human peripheral lymphocytes. *Mutation Res.* 654: 88-92.
310. Carpenter DO and Sage C (2008) Setting prudent public health policy for electromagnetic field exposures. *Rev Environ Health* 23: 91-117.
311. Neagu B, Strominger NL and Carpenter DO (2008) Contribution of NMDA receptor-mediated component to the EPSP in mouse Schaffer collateral synapses under single pulse stimulation protocol. *Brain Res.* 1240: 54-61.
312. Holdren J, Tao S and Carpenter DO (2008) Environment and health in the 21<sup>st</sup> Century: Challenges and solutions. *Ann NY Acad Sci.* 1140:1-21.
313. Carpenter DO, Ma J and Lessner L (2008) Asthma and infectious respiratory disease in relation to residence near hazardous waste sites. *Ann NY Acad Sci.* 1140: 201-208.
314. Sandal S, Tuneva J, Yilmaz B and Carpenter DO (2009) Effects of cholesterol and docosahexaenoic acid on cell viability and (Ca<sup>2+</sup>)<sub>i</sub> levels in acutely isolated mouse thymocytes. *Cell Biochem Funct* 27: 155-161.
315. Steele RE, de Leeuw, E and Carpenter DO (2009) A novel and effective treatment modality for medically unexplained symptoms. *J Pain Management* 1: 402-412
316. Sage C and Carpenter DO (2009) Public health implications of wireless technologies. *Pathophysiology* 16: 233-246.
317. Sly PD, Eskenazi B, Pronczuk J, Sram R, Diaz-Barriga F, Machin DG, Carpenter DO, Surdu S and Meslin EM (2009) Ethical issues in measuring biomarkers in children's environmental health. *Environ Health Perspect.* 117: 1185-1190.
318. Goncharov A, Rej R, Negoita S, Schymura M, Santiago-Rivera A, Morse G, Akwesasne Task Force on the Environment and Carpenter DO (2009) Lower serum testosterone associated with elevated polychlorinated biphenyl concentrations in Native American men. *Environ Health Perspect.* 117:1454-1460.
319. Tuneva JO, Karpova LV, Shittur SV, Carpenter DO, Johnson P and Boldyrev AA (2009) Amyloid- $\beta$  and aluminum ions enhance neuronal damage mediated by NMDA-activated glutamate receptors. *Biochemistry (Moscow) Supplement Series A: Membrane and Cell Biology* 4: 466-471.
320. Carpenter DO and Nevin R (2009) Environmental causes of violence. *Physiol Behavior* 99: 260-268.
321. Goncharov A, Bloom MS, Pavuk M, Carpenter DO for the Anniston Environmental Health Research Consortium. (2009) Exposure to PCBs and hypertension in the Anniston Community Health Survey. *Organohal Comp* 71: 0-136.
322. Sergeev AV and Carpenter DO (2010) Residential proximity to environmental sources of persistent organic pollutants and first-time hospitalizations for myocardial infarction with

- comorbid diabetes mellitus: A 12-year population-based study. *Int J Occup Med Environ Health* 23: 5-13.
323. Carpenter DO (2010) Electromagnetic fields and cancer: The cost of doing nothing. *Rev Environ Health* 25: 75-80.
  324. Sergeev AV and Carpenter DO (2010) Exposure to persistent organic pollutants increases hospitalization rates for myocardial infarction with comorbid hypertension. *Primary Prevention Insights*. 2: 1-9.
  325. Hori N, Kadota MT, Watanabe M, Ito Y, Akaike N and Carpenter DO (2010) Neurotoxic effects of methamphetamine on rat hippocampus pyramidal neurons. *Cell Mol Neurobiol* 30: 849-856.
  326. Hardell, S, Tilander H, Welfinger-Smith G and Carpenter DO (2010) Levels of polychlorinated biphenyls (PCBs) and three organochlorine pesticides in fishes from the Aleutian Islands of Alaska. *PLoS ONE*, 5:e12396.
  327. Carpenter, DO. (2010) Human health effects of EMFs: The cost of doing nothing. *IOP Conf. Series: Earth and Environmental Science* 10: 012004. doi:10.1088/1755-1315/10/1/10/012004.
  328. Goncharov A, Bloom M, Pavuk M, Birman I and Carpenter DO for the Anniston Environmental Health Research Consortium. Blood pressure and hypertension in relation to levels of serum polychlorinated biphenyls in residents of Anniston, Alabama. *J Hypertension*. 28: 2053-2060..
  329. Prasad A, Ahs M, Goncharov A and Carpenter DO (2010) Omega-3 and omega-6 fatty acids kill thymocytes and increase membrane fluidity. *The Open Cell Development & Biology Journal* 3: 1-8
  330. Sergeev AV and Carpenter DO (2010) Increased hospitalizations for ischemic stroke with comorbid diabetes and residential proximity to source of organic pollutants: A 12-year population-based study. *Neuroepidemiology* 35:196-201.
  331. Prasad A, Bloom M and Carpenter DO (2010) Role of calcium and ROS in cell death induced by polyunsaturated fatty acids in murine thymocytes. *J Cell Physiol*. 225: 829-836.
  332. Sergeev AV and Carpenter DO (2010) Geospatial patterns of hospitalization rates for stroke with comorbid hypertension in relation to environmental sources of persistent organic pollutants: Results from a 12-year population-based study. *Environ Sci Pollut Res Int* 18: 576-585.
  333. Brown D, Goncharov A, Paul E, Simonin H and Carpenter DO. (2010) The relationships between Adirondack lake pH and levels of mercury in yellow perch. *J Aquat Animal Health*. 22:280-290.
  334. Gavidia T, Brune M-N, McCarty KM, Pronczuk J, Etzel R, Neira M, Carpenter DO, Suk WA, Arnold RG, Ha EH, and Sly PD (2010) Children's environmental health – from knowledge to action. *Lancet* 377:1134-1136.
  335. Bushkin-Bedient S and Carpenter DO (2010) Benefits versus risks associated with consumption of fish and other seafood. *Rev Environ Health* 25: 161-191.
  336. Goncharov A, Pavuk M, Foushee HR and Carpenter DO for the Anniston Environmental Health Consortium (2010) Blood pressure in relation to concentrations of PCB congeners and chlorinated pesticides. *Environ Health Perspect*. 119:319-325.
  337. Yilmaz B, Sandal S and Carpenter DO (2010) PCB 9 exposure induces endothelial cell death while increasing intracellular calcium and ROS levels. *Environ Toxicol*. In press. doi: 10.1002/tox.20676.

338. Sly PD, Arnold RG and Carpenter DO (2011) Environmental exposures in the era of climate change. *Rev Environ Health* 26: 1-4.
339. Carpenter DO (2011) Health effects of persistent organic pollutants: The challenge for the Pacific Basin and for the World. *Rev Environ Health* 26: 61-69.
340. Sergeev AV and Carpenter DO (2011) Increase in metabolic syndrome-related hospitalizations in relation to environmental sources of persistent organic pollutants. *Int J Environ Res Public Health* 8:762-776.
341. Carpenter DO, Miller PK, Waghiyi, Welfinger-Smith G (2011) Environmental contamination of the Yupik people of St. Lawrence Island, Alaska. *J Indigenous Res In Press*.
342. Carpenter DO (2010) Human health effects of EMFs: The cost of doing nothing. *IOP C Ser Earth Env* 10:1-6.
343. Kamalov J, Carpenter DO, Birman I (2011) Cytotoxicity of environmentally relevant concentrations of aluminum in murine thymocytes and lymphocytes. *J Toxicol*. Doi:10.1155/2011/796719.
344. Silbernagel S, Carpenter DO, Gilbert SG, Gochfeld M, Groth E, Hightower JM, Schiavone FM. (2011) Recognizing and preventing over exposure to methylmercury from fish and seafood consumption: Information for physicians. *J Toxicol*, 2011; doi:10.1155/2011/983072
345. Welfinger-Smith G, Minholz JL, Byrne S, Waghiyi V, Golodergren J, Kava J, Apatiki M, Ungott E, Miller PK, Arnason J and Carpenter DO. (2011) Organochlorine and metal contaminants in traditional foods from St. Lawrence Island, Alaska. *J Toxicol Environ Health A*. 74: 1-20.
346. Åhs M, Prasad A, Aminov Z and Carpenter DO (2011) Mechanisms of cell death of thymocytes induced by polyunsaturated, monounsaturated and trans-fatty acids. *J Cell. Biochem*. In press.
347. Boberg E, Lessner L and Carpenter DO. The role of residence near hazardous waste sites containing benzene in the development of hematologic cancers in upstate New York. *Int J Occup Med Environ Health*. In press.
348. Turyk ME, Bhazsar SP, Bowerman W, Boysen E, Clark M, Diamond M, Mergler D, Pantazopoulos P, Schantz S and Carpenter DO (2011) Risks and benefits of consumption of Great Lakes fish. *Environ Health Perspect*. In press.
349. Ma J, Lessner L, Schreiber J and Carpenter DO (2009) Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York city. *J Environ Public Health* doi:10.1155/2009/183920.

#### **Books:**

1. Cellular Pacemakers I: Mechanisms of Pacemaker Generation, David O. Carpenter, editor; John Wiley & Sons, New York, 1982.
2. Cellular Pacemakers II: Function in Normal and Disease States, David O. Carpenter, editor; John Wiley & Sons, New York 1982.
3. Biologic Effects of Electric and Magnetic Fields, Volume I: Sources and Mechanisms of Biologic Effects, David O. Carpenter and Sinerik Ayrapetyan, editors; Academic Press, California, 1994.

4. Biologic Effects of Electric and Magnetic Fields, Volume II: Beneficial and Harmful Effects, David O. Carpenter and Sinerik Ayrapetyan, editors; Academic Press, California, 1994.
5. Environmental Challenges in the Pacific Basin, David O. Carpenter, ed. New York Academy of Sciences, Vol 1140, 457 pp, 2008.

#### Reviews and Book Chapters:

1. Carpenter, D.O. Ionic mechanisms and models of endogenous discharge of *Aplysia* neurons. Proceedings of the Symposium on Neurobiology of Invertebrates: Mechanisms of Rhythm Regulation. Tihany, Hungary, August 2-5, 1971, Hungarian Academy of Sciences, pp. 35-58, 1973.
2. Carpenter, D.O., Hovey, M.M. and Bak, A.F. Measurements of intracellular conductivity in *Aplysia* neurons: Evidence for organization of water and ions. Ann. NY Acad. Sci., 204:502-533, 1973.
3. Carpenter, D.O., Hubbard, J.H., Humphrey, D.R., Thompson, H.K. and Marshall, W.H. CO<sub>2</sub> effects on nerve cell function. In: Topics in Environmental Physiology and Medicine: Carbon Dioxide and Metabolic Regulation. (Eds.: G. Nahas and K.A. Schaefer), Springer-Verlag, New York, pp. 49-62, 1974.
4. Parmentier, J. and Carpenter, D.O. Blocking action of snake venom neurotoxins at receptor sites to putative central nervous system transmitters. In: Animal, Plant and Microbial Toxins (Eds.: A. Ohaska, K. Hayashi, and Y. Sawai), Plenum Press, London, Vol. 2, pp. 179-191, 1976.
5. Pierau, Fr.-K. and Carpenter, D.O. Metabolic control of peripheral temperature receptors in the scrotal skin of the rat. Israel J. Med. Sci., 12:1044-1046, 1976.
6. Carpenter, D.O. Membrane Excitability: In: Mammalian Cell Membranes Vol. 4, Membranes and Cellular Functions, (Eds.: G.A. Jamieson and D.M. Robinson), Butterworth & Co., London, pp. 184-206, 1977.
7. Carpenter, D.O., Myers, P.R., Shain, W., Sinback, C.N. and Swann, J.W. Interchangeable association of neurotransmitter receptors and ionophores in vertebrate and invertebrate cells. Proc. Symposium: "Ionophoresis and Transmitter Mechanisms in the Mammalian Central Nervous System", Cambridge, England, Raven Press, pp. 203-205, 1978.
8. Carpenter, D.O., McCreery, M.J., Woodbury, C.M. and Yarowsky, P.J. Modulation of endogenous discharge in neuron R-15 through specific receptors for several neurotransmitters. In: Abnormal Neuronal Discharges, (Eds: N. Chalazonitis and M. Boisson), Raven Press, New York, pp. 189-203, 1978.
9. Tsien, R.W. and Carpenter, D.O. Ionic mechanisms of pacemaker activity in cardiac purkinje fibers. Fed. Proc., 37:2127-2131, 1978.
10. Keabian, P.R., Keabian, J.W. and Carpenter, D.O. Serotonin causes accumulation of cyclic AMP in *Aplysia* hear. The Proceedings of the Fourth International Catecholamine Symposium, (Eds: E. Usdin and I. Kopin), Pergamon Press, New York, pp. 1167-1169.
11. Braitman, D.J., Aufer, C.R. and Carpenter, D.O. Direct and modulatory actions of thyrotropin-releasing hormone (TRH) in sensorimotor cortex. Proc. EMBO Workshop on Drug Receptors in the Central Nervous System, Weizman Institute of Science, Rehovot, Israel, February 10-14, 1980.



12. Carpenter, D.O. Ionic and metabolic bases of neuronal thermosensitivity. Fed. Proc., 40:2808-2813, 1981.
13. Carpenter, D.O. and Reese, T.S. Chemistry and Physiology of Synaptic Transmissions. In: Basic Neurochemistry, 3rd Edition, (Eds.: Siegel, Albers, Agranoff and Katzman), Little, Brown and Company, pp. 161-168, 1981.
14. Shain, W. and Carpenter, D.O. Mechanisms of synaptic modulation. Intl. Rev. Neurobiol., 22:205-247, 1981.
15. Wiederhold, M.L. and Carpenter, D.O. Possible Role of Pacemaker Mechanisms in Sensory Systems. In: Cellular Pacemakers II: Function in Normal and Disease States, (Ed.: D.O. Carpenter), John Wiley & Sons, New York, pp. 27-58, 1982.
16. Carpenter, D.O. The generator potential mechanism in cold afferents may be an electrogenic sodium pump. Workshop on Mechanisms of Thermal Regulations. I. Therm. Biol., 387-390, 1983.
17. Carpenter, D.O. and Gregg, R.A. Functional significance of electrogenic pumps in neurons. In: Electrogenic transport: Fundamental Principles and Physiological Implications, (Eds.: M. Blaustein and M. Liebermann), Raven Press, pp. 253-270, 1984.
18. Carpenter, D.O., Briggs, D.B. and Strominger, N. Behavioral and electrophysiological studies of peptide-induced emesis in dogs. Fed. Proc., 43:16-18, 1984.
19. Coyle, J.T., Blakeley, R.D., Zaczeck, R., Ory-Lavallee, L., Koller, K., ffrench-Mullen, J.M.H. and Carpenter, D.O. Acidic peptides in brain: Do they act at putative glutamatergic synapses. In: Excitatory Amino Acids and Epilepsy, (Eds.: Y. Ben-Ari and R. Schwarcz), Plenum Press, New York, pp. 375-384.
20. Carpenter, D.O., ffrench-Mullen, J.M.H., Hori, N., Sinback, C.N. and Shain, W. Segregation of synaptic function on excitable cells. In: Neural Mechanisms of Conditioning, (Eds.: D. Alkon and C.D. Woody), Plenum Press, NY, pp. 355-369, 1985.
21. Carpenter, D.O. and Hall, A.F. Responses of Aplysia cerebral ganglion neurons to leucine enkephalin. In: Comparative Aspects of Opioid and Related Neuropeptide Mechanisms, (Eds.: M. Leung and G. Stefano), CRC Press, pp. 49-57.
22. Zaczeck, R., Koller, K., Carpenter, D.O., Fisher, R., ffrench-Mullen, J.M.H. and Coyle, J.T. Interactions of acidic peptides: Excitatory amino acid receptors. In: Excitatory Amino Acids, (Ed.: P.J. Roberts), Macmillan, London, 1987.
23. Carpenter, D.O. Central nervous system mechanisms in deglutition and emesis. In: Handbook of Physiology, Section 6: The Gastrointestinal System. Vol. I, Motility and Circulation, (Ed.: J.D. Wood), American Physiological Society, Chapter 18, pp. 685-714, 1989.
24. Carpenter, D.O., Briggs, D.B. and Strominger, N. Mechanisms of radiation-induced emesis in the dog. Pharmacol. Ther., 39:367-371, 1988.
25. Carpenter, D.O. Comparative biology of neurotransmitter functions. Biology International, 15:2-9, 1987.
26. Carpenter, D.O. Electromagnetic Fields: Do We Know Enough to Act? In: Health and Environmental Digest, Vol. 2, pp. 3-4, 1988.
27. Carpenter, D.O. The New York State Power Lines Project: Summary and Conclusions. In: 20th Annual National Conference on Radiation Control, CRCPD Publication 88-6, Nashville, Tennessee, May 15-19, 1988, pp. 399-409.
28. S.-Rozsa, K., Carpenter, D.O., Stefano, G.B. and Salanki, J. Distinct responses to opiate peptides and FMRFamide on B-neurons of the Aplysia cerebral ganglia. In: Comparative

- Aspects of Neuropeptide Function, (Eds. E. Florey and G.B. Stefano), Manchester University Press, Chapter 6, pp. 73-86, 1991.
29. Carpenter, D.O. A common mechanism of excitation of area postrema neurons by several neuropeptides, hormones and monoamines. In: Comparative Aspects of Neuropeptide Function, (Eds. E. Florey and G.B. Stefano) Manchester University Press, Chapter 21, pp. 260-270, 1991.
  30. Carpenter, D. O., Hirotsu, I., Katsuda, N. and Hori, N. The effects of acetylcholine and aging on electrical excitability of the central nervous system. In: Neuroregulatory Mechanisms in Aging, Pergamon Press LTD, pp. 5-23, 1993.
  31. Turner, J.N., Swann, J.W., Szarowski, D.H., Smith, K.L., Shain, W., Carpenter, D.O. and Fejtl, M. Three-dimensional confocal light and electron microscopy of neurons: fluorescent and reflection stains. Methods in Cell Biology, 38:345-366, 1993.
  32. Deno, D. and Carpenter, D.O. Sources and characteristics of electric and magnetic fields in the environment. In: Biologic Effects of Electric and Magnetic Fields, Volume I: Sources and Mechanisms of Biologic Effects, David O. Carpenter and Sinerik Ayrapetyan, editors, Academic Press, California, pp. 3-59, 1994.
  33. Carpenter, D.O. The public health implications of magnetic field effects on biological systems. In: Biologic Effects of Electric and Magnetic Fields, Volume II: Beneficial and Harmful Effects, David O. Carpenter and Sinerik Ayrapetyan, editors, Academic Press, California, pp. 321-329, 1994.
  34. Carpenter, D.O. Multidisciplinary study of hazardous wastes at a Great Lakes Superfund Site. Great Lakes Research Review, 1: 37-39, 1994.
  35. Fejtl, M. and Carpenter, D.O. Single-channel studies in molluscan neurons. In: Ion Channels, Vol. 4, Toshio Narahashi, ed., Plenum Press, New York, pp. 333-376, 1996.
  36. Turner, J.N., Swann, J.W., Szarowski, D.H., Smith, K.L., Shain, W., Carpenter, D.O. and Fejtl, M. Three-dimensional confocal light and electron microscopy of central nervous system tissue, and neurons and glia in culture. In: International Review of Experimental Pathology, V.J. Savin and T.B. Wiegmann, editors, Volume 36, Academic Press, pp. 53-72, 1996.
  37. Boldyrev, A., Lawrence, D. and Carpenter, D. Effect of carnosine and its natural derivatives on apoptosis of neurons induced by excitotoxic compounds. In: Peptide Science-Present and Future, Y. Shimonishi, editor, Kluwer Academic Publishers, Great Britain, pp. 424-426, 1998.
  38. Carpenter, D.O., Hussain, R., Tan, Y., Niemi, W. and Hori, N. Long-term potentiation and long-term depression: Relevance to learning and memory. In: Modern Problems of Cellular and Molecular Biophysics. S.N. Ayrapetyan and A.C.T. North, editors, Nayan Tapan, pp. 83-94, 2001.
  1. Carpenter, D.O. NMDA receptors and molecular mechanisms of excitotoxicity. In: Oxidative Stress at Molecular, Cellular and Organ Levels, A. Boldyrev and P. Johnson, editors, Research Signpost, pp. 77-88, 2002.
  2. Carpenter, D.O. Clearing the air: Asthma an indoor exposure. INMA 96: 1-2, 2004.
  41. Carpenter DO. Environmental contaminants and human health: The health effects of persistent toxic substances. Firat Tip Dergisi 10: \_\_\_\_: 2005.
  42. Hermanson MH, Johnson GW and Carpenter DO. Routes of human exposure to PCBs in Anniston, Alabama. ACS Division of Environmental Chemistry, 232rd National Meeting, 46: 1117-1122, 2006

43. Carpenter DO and Welfinger-Smith G. The Hudson River: A case study of PCB contamination. In: Water and Sanitation-Related diseases and the Environment: Challenges, Interventions, and Preventative Measures. Janine M.H. Selendy, Ed., Wiley & Sons, Inc. 2011, pp 303-327.
44. Welfinger-Smith G and Carpenter DO. Addressing sources of PCBs and other chemical pollutants in water. In: Water and Sanitation-Related diseases and the Environment: Challenges, Interventions, and Preventative Measures. Janine M.H. Selendy, Ed., Wiley & Sons, Inc. 2011, pp 359-384.

#### Other Publications:

1. Barker, J.L. and Carpenter, D.O. Neuronal thermosensitivity. *Science*, 172:1361-1362, 1971.
2. Carpenter, D.O. Cellular Pacemakers. *Fed. Proc.*, 37:2125-2126, 1978.
3. Carpenter, D.O. Membrane biophysics and general neurobiology in Japan. *ONR Tokyo Scientific Bulletin*, 3:23-27, 1978.
4. Carpenter, D.O. Research on the primate nervous system in Japan. *ONR Tokyo Scientific Bulletin*, 3:28-32, 1978.
5. Carpenter, D.O. Report on the Sixth International Biophysics Congress, Kyoto, Japan. *ONR Tokyo Scientific Bulletin*, 3:38-40, 1978.
6. Carpenter, D.O. Interchangeable association of neurotransmitter receptors with several ionophores. *Brain Research Bulletin*, 4:149-152, 1978.
7. Carpenter, D.O. and Ahlbom, A. Power lines and cancer: Public health and policy implications. *Forum*, 3:96-101, 1988.
8. Carpenter, D.O. Setting Health Policy When the Science and the Risk are Uncertain. In: *The Scientific Basis of Health Policy in the 1990s*, Proceedings of the School of Public Health's Fifth Anniversary Symposium, 54-63, 1990.
9. Carpenter, D.O. Integrating public health in professional education. *Optometry and Vision Science*, 70: 699-702, 1993.
10. Bowerman, W.W., Carey, J., Carpenter, D.O., Colborn, T., DeRosa, C., Fournier, M., Fox, G.A., Gibson, B.L., Gilbertson, M., Henshel, D., McMaster, S. and Upshur, R. Is it time for a Great Lakes Ecosystem Agreement separate from the Great Lakes Water Quality Agreement? *J. Great Lakes Res.* 25:237-238, 1999.
11. Carpenter, D.O. Editorial Comment of APrimary hypoxic tolerance and chemical preconditioning during estrus cycle@. *Stroke*, 30:1262, 1999.
12. Carpenter, D.O. Bring environmental health back into public Health. *J. Pub. Health Mgmt. Pract.*, 5:vii-viii, 1999.
13. Carpenter, D.O. Should children and women of childbearing age eat Great Lakes fish? *Great Lakes Commission Advisor*, 13: 8, 2000.
14. Hites, R.A., Foran, J.A., Schwager, S.J., Knuth, B.A., Hamilton, M.C. and Carpenter, D.O. Response to comment on AGlobal Assessment of Polybrominated Diphenyl Ethers in Farmed and Wild Salmon@. *Environ. Sci. Technol.* 39: 379-380.
15. Carpenter, D.O. Blood lead and IQ in older children. Letter to the editor. *Environ. Health Perspect.*, 113: A581-A582, 2005.

16. Foran, J.A., Carpenter, D.O., Good, D.H., Hamilton, M.C., Hites, R.A., Knuth, B.A. and Schwager, S.J. Risks and benefits of seafood consumption. Letter to the editor. Am.J. Prev. Med. 30: 438-439, 2006.

#### **PREVIOUS DEPOSITIONS AND TESTIMONY (past seven years):**

Antonia Tolbert et al. vs. Monsanto Company, Pharmacia Corp., and Solutia Inc.,  
deposed for the plaintiffs, 21-22 January 2003. Mark Englehart, Attorney 334-269-2343.

Aaron et al. vs. Chicago Housing Authority et al., deposed for the plaintiffs, 5-6 March  
2003.

Kellum et al., vs. Kuhlman Corporation, deposed for the plaintiffs, 4 September 2004.  
Douglas Mercier, Attorney, 601-914-2882.

Allgood et al. vs. General Motors Corporation, deposed for the plaintiffs, 8-10 December  
2004. Brian J. Leinbach, Attorney. 310-552-3800.

Maggie T. Williams et al. vs. Kuhlman Corporation, deposed for the plaintiffs, 1  
February and 25 February 2005. Douglas Mercier, Attorney, 601-914-2882.

Solutia Inc. et al., Debtors, vs. Monsanto Company and Pharmacia Corporation; deposed  
for the plaintiffs, 12 September 2006. Samuel E. Stubbs, Attorney; 713-425-7345.

Charles W. Adams, et al., vs. Cooper Industries, Inc. et al., deposed for the plaintiffs, 28-  
29 September 2006. Donna Keene Holt, Attorney. 865-212-3294.

Arthur D. Dyer et al. vs. Waste Management et al., deposed for the plaintiffs, 2  
November 2006. Mark L. Thomsen, Attorney. Cannon & Dunply, Brookfield, WI 53008.

Clopten et al. vs. Monsanto, deposed for the plaintiffs, 31 January 2007. Robert Roden,  
Attorney. 406-525-2665.

Marty Paulson et al. vs. Monsanto, deposed for the plaintiffs, 7 August 2007. Torger  
Oaas, Attorney. 406-525-2665.

John Edward Martinez and Gladys Yolanda Martinez vs. Entergy Corporation et al.,  
deposed for the plaintiffs, 16 April 2008. Julie Jacobs, Attorney. 504-566-1704.

Fannie Wayne et al. vs. Pharmacia Corporation, et al., deposed for the plaintiffs, 29  
October 2008. John E. Norris, Attorney. 205-541-7759.

Fannie Wayne et al. vs. Pharmacia Corporation et al., testified for the plaintiffs, 31  
March-1 April, 2009. John E. Norris, Attorney. 205-541-7759.

Clement Passariello, et al., vs. CL&P, et al.; William Korzon, et al., vs. CL&P, et al.;  
Louis Gherlone et al., vs. CL&P, et al.; and William Ho, et al., vs. CL&P et al., deposed for the  
plaintiffs, 13 April 2009. Benson A. Snader, Attorney. 203-777-6426.

Before the Pennsylvania Public Utility Commission, docket No A-2009-2082652, et al.  
Testified on behalf of the Saw Creek Estates Community Association, 2 September 2009. Paul  
M. Schmidt, Attorney. 215-569-2800 x161.

James Alford et al. v. Kuhlman Corporation, et al., pending in the USDC, Southern  
District of Mississippi, Deposed for plaintiffs, 20 August 2009. Shiela Bossier, Attorney. 601-  
352-5450

Fannie Wayne et al. v. Pharmacia Corporation. Deposed for plaintiffs, 23 September  
2009, Timothy C. Davis, Attorney. 205-327-9115.

Before the Minnesota Public Utilities Commission in the matter of the route permit  
application by Great river energy and Xcel Energy for a 345 kV transmission line from  
Brookings County, South Dakota to Hampton, Minnesota. Testified for plaintiffs, 16 December

2009. Paula Maccabee, Attorney. 651-775-7128.

Highland Lakes Estates et al.v. Republic Services of Florida et al., Deposed for the plaintiffs, 23 April 2010. John W. Frost II, Attorney. 863-533-8985.

Zina G. Bibb, et al. v Monsanto Company et al. Deposed for plaintiffs, 28 April 2010. W. Stuart Calwell, Attorney, 304-343-4323.

Highland Lakes Estates et al., v. Republic Services of Florida et al., Testified for the plaintiffs, 13 May 2010.

Nora Williams, et al., v. City of Jacksonville, et al. Deposed for the plaintiffs.15 July 2010. Samuel W. Wethern, Attorney.

Ronald Cybart et al., Michael Campanelli, and Donald and Theresa Shea, et al.v. CL&P. Deposed for the plaintiffs. 15 July 2011. Benson A. Snaider, Attorney.

Maria Snoops vs. Lyon Associates, Inc. and Insurance Co of the state of Pennsylvania. Deposed for the plaintiff, 1 November 2011. Matthew J. Witteman, Attorney. 415-363-3106.

John Edward Martinez and Gladys Yolanda Martinez v. Entergy Corporation, et al., Deposed for the plaintiff, 19 December 2011. J. Patrick Connick, Attorney. 504-347-4535.